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VOLUME 1 1957

PERGAMON PRESS LTD.

LONDON NEW YORK PARIS LOS ANGELES

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FOREWORD

WITH the publication of this first part of Volume 1, a significant and unique enterprise has been launched. The special character claimed for TETRAHEDRON is its fully international scope, since the new journal is envisaged as a forum for the presentation of original memoirs on organic chemistry contributed from all parts of the world.

Without disparagement of the papers herein it must be pointed out that the first number of a new journal must perforce rely on a limited number of enthusiastic authors and the publishers must be content to accept that which lies immediately at hand. We are convinced that the quality of TETRAHEDRON will bear comparison with that of any other medium of publication and it is the firm intention of the honorary editorial advisory board and that of the editors and publishers to achieve this.

The papers may deal with any aspect of pure organic chemistry and also with applied organic chemistry, always provided that some scientific advance forms part of the subject matter. It is anticipated that the great majority of contributions will be in the fields of "classical" organic chemistry, or one of the physical aspects which are of so much, and increasing, importance today. The usual type of original paper is naturally most welcome, but, in view of the desirability of an increase of understanding of the work of colleagues in other countries, papers with some original content may well include longer historical introductions than is customary in the national journals. In addition, longer papers in which the results of extended investigations are described in a unified manner will be considered appropriate.

Papers may be presented as "Notes" or "Preliminary Communications," and the latter need not be limited to very short statements.

The ideal which activates this initiative is based on our conviction that science is a worldwide discipline, and we hope to do a real service to international collaboration in organic chemistry.

Robert Robinson

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Tetrahedron, 1957, Vol. 1, pp. 3–8. Pergamon Press Ltd., London

ALICYCLIC STUDIES—X*

THE BICYCLO-(5:4:0)-2-UNDECANONES

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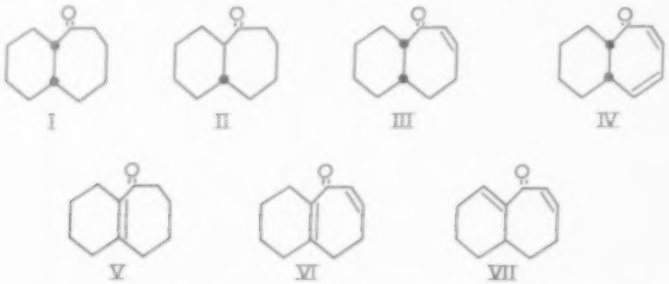
(*Received* 20 *September* 1956)

Abstract—The stereochemistry of the bicyclo-(5:4:0)-2-undecanones is discussed. The cis-*ketone* is obtained by catalytic reduction of benzosuberone and is converted into the trans-*ketone* by treatment with sodium methoxide. Dehydrogenation experiments of both isomers are described.

IN the α-hydrindanone system the *cis* isomer is known to be conformationally more stable than the *trans* compound.[2] In the α-decalone system the reverse situation obtains.[3] It was of interest to determine the relative stabilities of the next higher homologues, the bicyclo-(5:4:0)-2-undecanones (hexahydrobenzosuberones).

The aromatic ring of benzosuberone cannot be hydrogenated in the presence of Adams catalyst without concomitant reduction of the carbonyl group and hydrogenolysis of the resulting benzyl-type alcohol.[4] It was found that a quantitative yield of *cis*-bicyclo-(5:4:0)-2-undecanol can be obtained by employing ruthenium oxide as the hydrogenation catalyst. This alcohol clearly does not suffer hydrogenolysis in the presence of ruthenium and can be oxidised in high yield by means of chromic anhydride in acetic acid to the cis-*ketone*(I). This ketone does not isomerise under



the conditions employed for formation of its oxime, semicarbazone, or 2:4-dinitrophenylhydrazone, but it can be isomerised to the trans-*ketone*(II) by treatment with sodium methoxide. The trans-*ketone* affords a different set of derivatives from that given by its *cis* isomer.

It is important to note that the same alcohol results on catalytic reduction of benzosuberone and benzosuberol, thus ruling out any possibility of a mechanism of 1:4-reduction in the case of the ketone.

* Part IX *J. Chem. Soc.* 1301 (1957).

[1] Presented at XIVth Congress of the International Union of Pure and Applied Chemistry, Zurich, July 1955. *Abstr. of Congress*, p. 49.

[2] E. L. Eliel and C. Pillar *J. Amer. Chem. Soc.* **77**, 3600, who also gives leading references (footnote 3) (1955).

[3] W. Hückel and E. Brinkmann *Annalen* **441**, 21 (1925).

[4] Pl. A. Plattner *Helv. Chim. Acta* **27**, 801 (1944).

Dehydrogenation experiments were carried out both with the *cis*- and *trans*-bicyclo-(5:4:0)-2-undecanones. Thus, when the cis-*ketone* was treated with 1 mole of selenium dioxide, a monoenone, formulated as (III), was obtained. When the latter was treated with 1 mole of *N*-bromosuccinimide followed by dehydrobromination or when the cis-*ketone* was treated with two moles of selenium dioxide, the same product, a dienone, formulated as (IV), was obtained. Further treatment of the dienone with *N*-bromosuccinimide had no effect.

Clearly the molecular shape of the cis-*ketone* does not permit attack of any of the above reagents at the ring junction; even after two double bonds had been introduced, the driving force of potential formation of a tropone derivative is not sufficient to counteract this geometrical influence.

In the case of the trans-*ketone*, however, excess of selenium dioxide (2 moles) introduces only one double bond, presumably at the junction of both rings. Here no similar hindrance exists, and the first step is probably hydroxylation at the tertiary ring junction α to the carbonyl group and ready *trans* elimination of water is possible with the formation of (V). Treatment of this product with *N*-bromosuccinimide followed by dehydrobromination leads to a cross-conjugated dienone (VI) or (VII). (See experimental section for spectroscopic data upon which these formulations are based.)

EXPERIMENTAL*

cis-*Bicyclo*-(5:4:0)-2-*undecanol*

Benzosuberone[5] (10 g) in ethyl acetate (100 ml) was hydrogenated in the presence of ruthenium oxide (0·7 g) at an initial pressure of 1000 lb/sq. in. and 80°C. Hydrogen uptake (4 moles) stopped after 2·5 hr. After removal of the catalyst by filtration and the solvent by distillation, the *alcohol* was distilled, b.p. 112–113°/3 mm n_D^{25} 1·5078. Infra-red absorption (CCl_4): 3610 cm^{-1} (OH). Ultra-violet absorption: none (Found: C, 78·2; H, 12·0. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%).

The p-*nitrobenzoate* formed colourless crystals, m.p. 122–123° (from methanol-chloroform) (Found: C, 68·2; H, 7·9; N, 4·4. $C_{18}H_{23}NO_4$ requires C, 68·1; H, 7·3; N, 4·4%).

Careful fractionation of 50 g of the alcohol at 20 mm using a 25-plate column gave several preliminary fractions which gave a strong coloration with tetranitromethane (1 g), which evidently formed by partial dehydration of the alcohol during the distillation. The distillate was then divided into twelve fractions which boiled in the range 147–152°/20 mm and had n_D^{25} in the range 1·5076–1·5082. *p*-Nitrobenzoates of the first and last of these fractions both had m.p. 122–123° (from methanol-chloroform) and showed no depression in melting-point on admixture. No separation could therefore be accomplished between the possible axial and equatorial alcohols, and it appears that only the α-ol was formed in the hydrogenation.

cis-*Bicyclo*-(5:4:0)-2-*undecanone*

cis-Bicyclo-(5:4:0)-2-undecanol (100 g) was dissolved in acetic acid (A.R.; 200 ml), cooled in an ice-bath and a solution of chromic acid (A.R.; 44 g; 1·1 mole) in water (20 ml), and acetic acid (100 ml) was added over a period of 1 hr with cooling and stirring. The mixture was allowed to stand overnight at room temperature, and

* Melting- and boiling-points are uncorrected.

[5] R. C. Gilmore jr. and W. J. Horton *J. Amer. Chem. Soc.* **73**, 1413 (1951).

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methanol (5 ml) was added. After careful neutralisation with solid sodium bicarbonate, water was added and the solution was extracted with ether. After working up in the usual way, distillation afforded a forerun, b.p. below 78°/1 mm (3 g); and the ketone, b.p. 78–82°/1 mm (79 g), and a further quantity of the ketone, b.p. 82–90°/1 mm (17 g). The middle fraction was cooled in an alcohol–dry-ice bath, and two-thirds of the solidified product was allowed to melt and the liquid portion was decanted. The residue was allowed to melt and was refrozen. When two-thirds had again melted, the liquid was decanted and the residue which is pure *cis-ketone* had n_D^{25} 1·4930; d_4^{25} 0·9982 (Found: C, 79·9; H, 11·3. $C_{11}H_{18}O$ requires C, 79·5; H, 10·9%).

The orange 2:4-*dinitrophenylhydrazone* was prepared at room temperature and was recrystallised six times, from cold methanol-chloroform, m.p. 145–146° (Found: C, 59·3; H, 6·5; N, 16·3. $C_{17}H_{22}N_4O_4$ requires C, 58·9; H, 6·4; N, 16·2%).

The *oxime* formed colourless needles, m.p. 100–101° (from methanol) (Found: C, 72·8; H, 10·8; N, 7·2. $C_{11}H_{19}NO$ requires C, 72·9; H, 10·6; N, 7·7%).

The *semicarbazone* formed colourless crystals, m.p. 201–202° (from ethanol-chloroform) (Found: C, 65·0; H, 9·8; N, 18·6. $C_{12}H_{21}N_3O$ requires C, 64·5; H, 9·5; N, 18·8%).

trans-*Bicyclo*-(5:4:0)-2-*undecanone*

The isomerisation was carried out by dissolving cis-*ketone* (30 g) in a solution of methanol (100 ml) containing sodium methoxide (0·5 g). The solution was heated under reflux for 30 min, concentrated *in vacuo* to a volume of 50 ml, and poured into water. The mixture was neutralised with dilute hydrochloric acid and extracted with ether. After working up in the usual way, distillation afforded the trans-*ketone*, b.p. 72–74°/0·5 mm (27 g).

The product was recrystallised twice by freezing as described for the *cis*-isomer, and had n_D^{25} 1·4906, d_4^{25} 0·9856 (Found: C, 79·5; H, 11·3. $C_{11}H_{18}O$ requires C, 79·5; H, 10·9%).

The orange 2:4-*dinitrophenylhydrazone*, m.p. 173–174° (from methanol-chloroform) (Found: C, 58·8; H, 6·8; N, 16·1. $C_{17}H_{22}N_4O_4$ requires C, 58·9; H, 6·4; N, 16·2%).

The *oxime* formed colourless needles, m.p. 128–129° (from methanol) (Found: C, 73·0; H, 10·3; N, 7·7. $C_{11}H_{19}NO$ requires C, 72·9; H, 10·6; N, 7·7%).

The *semicarbazone* formed colourless crystals, m.p. 213–214° (from ethanol-chloroform) (Found: C, 65·0; H, 9·6; N, 19·1. $C_{12}H_{21}N_3O$ requires C, 64·5; H, 9·5; N, 18·8%).

Refluxing the trans-*ketone* in methanol containing a trace of sodium methoxide for longer periods of time (2-3 hr) has no effect and no dimerisation takes place during this period.

Benzylidene derivative of the trans-*ketone*

trans-*ketone* (2 g) and freshly distilled benzaldehyde were dissolved in methanol (20 ml), sodium methoxide (0·5 g) added, and the mixture was allowed to stand for 2 days in a stoppered flask at room temperature. Water was added until the solution just assumed turbidity, and the mixture was left standing overnight. The precipitate was removed by filtration and was recrystallised four times from methanol, giving long needles, m.p. 133–134° (Found: C, 79·6; H, 8·9. $C_{18}H_{22}O{\cdot}H_2O$ requires C, 79·4; H, 8·9%).

Sodium-alcohol reduction of trans-*ketone*

The trans-*ketone* (10 g) was dissolved in *n*-propanol (200 ml), the solution was heated to reflux, and sodium (20 g) was added in small pieces over a period of 2 hr. The solution was refluxed for an additional hour to ensure complete dissolution of the sodium. After working up in the usual way, distillation and redistillation afforded the trans-*bicyclo*-(5:4:0)-*undecan*-2β-*ol* (equatorial isomer), b.p. 113–114°/3 mm n_D^{25} 1·5002 (Found: C, 78·2; H, 11·6. $C_{11}H_{20}O$ requires C, 78·5; H, 12·0%).

The p-*nitrobenzoate* formed colourless crystals, m.p. 89–90° (from chloroform-methanol) (Found: C, 68·7; H, 8·1; N, 4·7. $C_{18}H_{23}NO_4$ requires C, 68·1; H, 7·3; N, 4·4%).

Hydrogenation with platinum oxide

The trans-*ketone* was hydrogenated in ethanol solution in the presence of Adams catalyst at room temperature and atmospheric pressure. After completion of hydrogen uptake (2 hr), the catalyst and solvent were removed and the α-*alcohol* was distilled in high vacuum, b.p. 83–84°/0·4 mm, n_D^{25} 1·4937. It was characterized as the p-*nitrobenzoate* which formed colourless needles, m.p. 87–87·5° (from chloroform-methanol). On admixture with the *p*-nitrobenzoate of the alcohol resulting from sodium-alcohol reduction of the trans-*ketone*, m.p. 89–90° (see above), the melting-point was depressed to 69–71°. The alcohol obtained by catalytic reduction is presumably the α-(axial) isomer.

Clemmensen-Martin reduction of trans-*ketone*

In a 1-litre three-necked flask fitted with a stirrer, gas-inlet tube, and reflux condenser, were placed freshly amalgamated granulated zinc (50 g), water (50 ml), and concentrated hydrochloric acid (100 ml). The mixture was heated to boiling with stirring and a solution of the trans-*ketone* (15 g) in toluene (50 ml) was slowly added. After 2, 6, 8, 12, 15, 18, and 20 hr the stirred boiling mixture was saturated with hydrogen chloride. All the zinc had dissolved, but the mixture on testing with 2:4-dinitrophenylhydrazine still contained ketone. More amalgamated zinc (10 g) was added, and the solution was again saturated with hydrogen chloride. No ketone remained at the end of 30 hr of heating.

The toluene layer was separated. The aqueous layer was almost neutralised with sodium carbonate solution, care being taken not to precipitate zinc hydroxide. The solution was extracted with ether, the ether and toluene solutions were combined, washed with dilute hydrochloric acid and with water, and dried over anhydrous sodium sulphate. The solvents were removed by distillation and the residue was distilled over potassium. The hydrocarbon had b.p. 130–140°/40 mm (13 g).

In order to remove any unsaturated material, the product was dissolved in acetic acid (A.R.; 50 ml), and chromic acid (A.R.; 0·5 g) in acetic acid (90%; 10 ml) was added. The solution was warmed on the steam bath for 2 hr and was worked up and separated into acidic and neutral fractions. The neutral fraction distilled at 105–115°/24 mm and was then carefully fractionated: forerun, b.p. 105–108°/24 mm (1 g); main fraction of trans-*bicyclo*-(5:4:0)-*undecane*, b.p. 108–109°/24 mm (9 g); third fraction, b.p. 109–114°/24 mm (2 g). The main fraction had n_D^{25} 1·4816; n_D^{20} 1·4836; d_4^{20} 0·9140 (Found: C, 86·9; H, 13·4. $C_{18}H_{20}$ requires C, 86·8; H, 13·2%). Plattner[4] reported for the *cis*-hydrocarbon d_4^{20} 0·9014; b.p. 88·5–89°/11 mm; n_D^{20} 1·4845.

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Hydrogenation of benzosuberol with ruthenium dioxide

Crystalline benzosuberol (5 g) was dissolved in ethyl acetate (40 ml) and hydrogenated in the presence of ruthenium dioxide (0·3 g) at an initial pressure of 930 lb/sq. in. at 80°. After 3 hr hydrogen uptake was complete and corresponded to 3 moles of hydrogen. After filtration of the catalyst and removal of the solvent, the alcohol was characterised as the *p*-nitrobenzoate, m.p. and mixed m.p. with the corresponding derivative obtained by catalytic reduction of benzosuberone (see above), 123–124°.

Oxidation of benzosuberol with pyridine-chromic acid complex

Benzosuberol (300 mg) in pyridine (3 ml) was added to chromic anhydride (300 mg) in pyridine (10 ml), and the mixture was allowed to stand overnight. After working up in the usual manner, the benzosuberone was characterized as its orange 2:4-*dinitrophenylhydrazone*, m.p. 213–214° (from chloroform-methanol), undepressed on admixture with an authentic sample. Ultra-violet absorption (chloroform): λ_{max} 3750 Å; ε 28,700 (Found: C, 59·8; H, 4·9; N, 16·8. $C_{17}H_{16}N_4O_4$ requires C, 60·0; H, 4·7; N, 16·5%).

Benzosuberone dioxolane

The substance was prepared in 85% yield by azeotropic distillation of a mixture of benzosuberone, ethylene glycol, and toluene in the presence of a trace of *p*-toluenesulphonic acid and working up in the usual way. It had m.p. 60–62° (from benzene) (Found: C, 76·5; H, 7·9. $C_{13}H_{16}O_2$ requires C, 76·4; H, 7·9%).

Dehydrogenation experiments with trans-*bicyclo*-(5:4:0)-2-*undecanol*

(a) A mixture of the trans-*ketone* (10 g) acetic anhydride (80 ml) and hydrated selenium dioxide (20 g) was heated under reflux for 3 hr. After the usual workup the *α,β-ethylenic ketone*(V), b.p. 128–132°/20 mm was obtained and characterised as the red 2:4-*dinitrophenylhydrazone*, flat needles, m.p. 170–171° (from ethyl acetate-ethanol). Ultra-violet absorption (chloroform): λ_{max} 3690 Å; ε_{max} 24,100 (Found: N, 16·4. $C_{17}H_{18}O_4N_4$ requires N, 16·4%). (b) The above product (3·2 g) was refluxed for 2 hr with *N*-bromosuccinimide (3 g; 1 mole) in dry carbon tetrachloride (25 ml). After the usual workup the residue was treated with lutidine to effect dehydrobromination and the *doubly-unsaturated ketone*(VI) or (VII) was distilled, b.p. 160–162°/30 mm n_D^{25} 1·5083. Ultra-violet absorption (chloroform): λ_{max} 2380 Å; ε_{max} 3320. Infra-red absorption (chloroform): 1692 cm^{-1}; 1615 cm^{-1}. It was characterized as the dark red 2:4-*dinitrophenylhydrazone*, needles, m.p. 191–192° (from chloroform-ethanol). Ultra-violet absorption (chloroform): λ_{max} 3760 Å; ε_{max} 27,400 (Found: N, 16·3. $C_{17}H_{16}O_4N_4$ requires N, 16·4%). The *semicarbazone* formed colourless crystals, m.p. 205–206° (from methanol). Ultra-violet absorption (EtOH): λ_{max} 2310 Å; ε_{max} 10,500.

Dehydrogenation experiments with cis-*bicyclo*-(5:4:0)-2-*undecanol*

(a) The cis-*ketone* was treated with 1 mole selenium dioxide, as described above for the trans-*ketone*. The *α,β-ethylenic ketone*(III) had b.p. 136–139°/20 mm, n_D^{25} 1·4916. Ultra-violet absorption (EtOH): λ_{max} 2410 Å; ε_{max} 9100. Infra-red absorption (CCl_4): 1697 cm^{-1}; 1620 cm^{-1}.

The *semicarbazone* formed colourless crystals, m.p. 190–191° (from methanol). Ultra-violet absorption: λ_{max} 2300 Å; ε_{max} 11,150 (Found: C, 65·0; H, 9·4; N, 19·0. $C_{12}H_{19}ON_3$ requires C, 65·1; H, 8·7; N, 19·0%).

The 2:4-*dinitrophenylhydrazone* formed red plates, m.p. 177–178° (from chloroform-methanol). Ultra-violet absorption (chloroform): λ_{max} 3715 Å; ε_{max} 26,700 (Found: N, 16·3. $C_{17}H_{18}O_4N_4$ requires N, 16·4%). (b) The *cis*-ketone was treated with 2 moles selenium dioxide, as described above. The doubly-unsaturated ketone(IV) was characterised as the *semicarbazone*, colourless crystals, m.p. 224–225° (from methanol), and the red 2:4-*dinitrophenylhydrazone*, m.p. 201–202°. Ultra-violet absorption (chloroform): λ_{max} 3810 Å; ε_{max} 22,000 (Found: C, 59·6; H, 5·8; N, 16·6. $C_{17}H_{16}O_4N_4$ requires C, 59·6; H, 5·3; N, 16·4%). The same ketone was obtained by treatment of the corresponding monoenone with 1 mole of *N*-bromosuccinimide. (c) Treatment of the dienone with *N*-bromosuccinimide followed by the usual workup yielded the unchanged dienone.

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Tetrahedron, 1957, Vol. 1, pp. 9–16. Pergamon Press Ltd., London

ALICYCLIC STUDIES—XI*

ATTEMPTED SYNTHESES OF 5:6-BENZAZULENE AND BENZHEPTALENES

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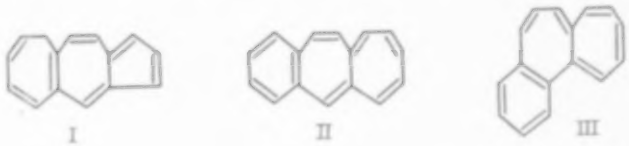
(*Received* 31 *December* 1956)

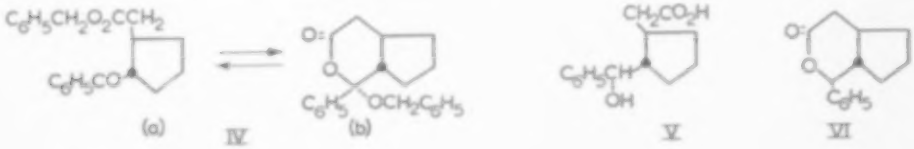
Abstract—1-Benzoylcyclopentene was used as starting material in an alicyclic approach towards the synthesis of 5:6-benzazulene. Bromination-dehydrobromination of the intermediate *trans*-1:2:3:4:9:10 hexahydrobenzazulene afforded a dibromo- and tetrabromo-derivative of 5:6-benzazulene. The bromination-dehydrobromination method is not feasible for the dehydrogenation of hydrobenzheptalenes to the as yet unknown benzheptalene system.

SUCCESSFUL alicyclic approaches to 4:5-benzazulene have been reported.[1, 2] 1-Benzoylcyclopentene appeared to be a useful starting material for the synthesis of the known 5:6-benzazulene[3] (I), while its seven-membered homologue might conceivably lead to the as yet unknown 2:3-benzheptalene (II). Another alicyclic intermediate, 2-phenylcyclohept-2-enone[4] might afford a route to 1:2-benzheptalene (III).



I II III

Michael condensation of 1-benzoylcyclopentene with dibenzyl malonate[5] afforded an adduct which upon debenzylation with hydrogen bromide in glacial acetic acid[6] at room temperature yielded the half ester. It is interesting that the monobenzyl ester (IVa) obtained upon decarboxylation exists in part in the form of the pseudo-ester (IVb) as evidenced by its infra-red spectrum. (See experimental section.) The same situation



(a) IV (b) V VI

* Part X. *Tetrahedron* **1**, (1957).
[1] J. R. Nunn and W. S. Rapson *J. Chem. Soc.* 1051 (1949).
[2] Y. Amiel, A. Löffler, and D. Ginsburg *J. Amer. Chem. Soc.* **76**, 3625 (1954).
[3] A. Plattner, A. Fürst and W. Keller *Helv. Chim. Acta* **32**, 2464 (1949).
[4] D. Ginsburg and R. Pappo *J. Amer. Chem. Soc.* **75**, 1094 (1953).
[5] D. Ginsburg *J. Chem. Soc.* 2361 (1954).
[6] D. Ben-Ishai and A. Berger *J. Org. Chem.* **17**, 1564 (1952).

obtains in the seven-membered ring homologue (see below). Complete debenzylation can be effected by employing the acidic reagent at elevated temperature. Decarboxylation of the malonic acid thus obtained followed by Huang-Minlon reduction afforded *trans*-2-benzylcyclopentylacetic acid.[5]

On one occasion, when catalytic hydrogenolysis of the dibenzyl ester was attempted,[4] decarboxylation of the acidic reaction products led to a mixture of acidic material (*trans*-2-benzoylcyclopentylacetic acid) and neutral material. It was clear from the behaviour of the latter on alkaline treatment and from its infra-red spectrum that this was a δ-lactone (absorption at 1746 cm^{-1}). Presumably the ketonic function was reduced in part of the material undergoing hydrogenolysis and the unisolated *trans*-acid (V) afforded the crystalline δ-lactone (VI). That this was indeed the case was shown by lithium aluminium hydride reduction to the crystalline *trans*-diol (VII).

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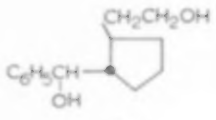
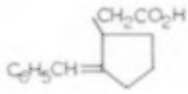
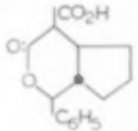


VII

VIII



IX



X

Further evidence on this point was sought by sodium borohydride reduction of IVa or of the corresponding free acid, *trans*-2-benzoylcyclopentylacetic acid. Thus, it was hoped that the hydroxy-ester or hydroxy-acid (V) would lead to the same lactone (VI). However, the hydroxy-ester upon alkaline saponification was converted into the same *stable* hydroxy-acid which was formed directly by sodium borohydride reduction of *trans*-2-benzoylcyclopentylacetic acid. Whilst a δ-lactone was formed during decarboxylation of the hydrogenolysis reaction mixture, the pure hydroxy-acid (V) upon treatment with naphthalene-β-sulphonic acid gave a γ-lactone (VIII) (infra-red absorption at 1765 cm^{-1}). The two five-membered rings in the γ-lactone must be *cis*-fused for steric reasons so that the *trans*-product formed after Michael condensation must eventually pass through the intermediate (IX) in which the *trans*-stereochemistry is destroyed. That the driving force in this reaction is the formation of the more stable γ-lactone was shown by refluxing the δ-lactone with sulphuric acid in acetic acid. The latter was quantitatively converted to a product whose infra-red spectrum was identical with that of the γ-lactone. The formation of the δ-lactone may be finally rationalised by the suggestion that it is not formed by lactonization of (V) after decarboxylation of the hydrogenolysis reaction mixture, but rather that X is formed in the hydrogenolysis mixture from the hydroxy-malonic acid and this upon decarboxylation affords the δ-lactone (VI). Since the employment of hydrogen bromide in glacial acetic acid became the method of choice for debenzylation, the structures of the lactones were not further investigated.

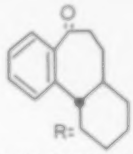
Polyphosphoric acid converted *trans*-2-benzylcyclopentylacetic acid into *trans*-7 oxo-1:2:3:4:7:8:9:10-octahydro-5:6-benzazulene in quantitative yield.[7] Sodium borohydride reduction afforded the corresponding alcohol,[7] and dehydration of the latter gave *trans*-1:2:3:4:9:10-hexahydrobenzazulene (XI).

[7] J. W. Cook, N. A. McGinnis, and S. Mitchell *J. Chem. Soc.* 286 (1944). See also ref. 5.

Rather than employing a high-temperature dehydrogenation method, stepwise bromination-dehydrobromination of this olefin was attempted. It soon became clear, however, that even when only one mole of *N*-bromosuccinimide is used, completely dehydrogenated products are obtained. After this bromination, chromatography on

XI

XII



XIII (a) R = H_2
(b) R = O

alumina permitted recovery of the major portion of the starting material (XI) and isolation of an alicyclic bromo-derivative and two bromo-derivatives of 5:6-benzazulene, a deep-purple dibromo-compound and a green-violet tetrabromo-derivative. On the basis of Anderson's work on bromination of azulene,[8] the dibromo-derivative is tentatively formulated as 1:3-dibromo-5:6-benzazulene.

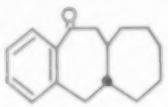
Concurrently with the work described above, 1-benzoylcycloheptene was analogously converted to the corresponding olefin, *trans*-1:6:7:8:9:10:11:12-octahydro-2:3-benzheptalene (XII). Furthermore, *trans*-3-oxo-2-phenylcycloheptylacetic acid[4] was converted by the Arndt-Eistert procedure to the corresponding keto-propionic acid and a small quantity of unreacted starting material was removed by treatment with anhydrous hydrogen fluoride. The substituted acetic acid is quantitatively cyclised to yield a neutral diketone,[4] whereas the keto-propionic acid is unaffected by this reagent. The keto-propionic acid was then cyclised by means of polyphosphoric acid to give *trans*-3:10-dioxo-3:4:5:6:7:8:9:10:11:12-decahydro-1:2-benzheptalene (XIIIb). *trans*-2-Phenylcycloheptylpropionic acid was similarly cyclised to the monoketone, XIIIa. Since *trans*-adducts are obtained in the Michael condensation of 2-aryl-cycloalk-2-enones[2, 4, 9] and since the stereochemistry would remain unchanged during the Arndt-Eistert reaction,[10] the propionic acids and XIIIa and XIIIb described above still maintain *trans*-stereochemistry. Ketone XIIIa and the isomeric product prepared by Gutsche[11] are both oils, but they give different semicarbazones (see experimental section). Gustsche's isomer must therefore be the *cis*-compound.

Bromination of XII under various reaction conditions, followed by dehydrobromination, led to an intractable mixture of bromo-derivatives. This method was therefore abandoned in the attempt to obtain 1:2- and 2:3-benzheptalene. Other methods to effect the synthesis of these as yet unknown compounds, are under investigation.

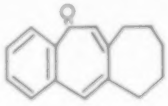
Bromination of *trans*-4-oxo-1:4:5:6:7:8:9:10:11:12-decahydro-2:3-benzheptalene (XIV) with one mole of *N*-bromosuccinimide followed by dehydrobromination, afforded a ketone (XV) in addition to recovered starting material, which is formulated as a tropone even though it forms a 2:4-dinitrophenylhydrazone. A study of models

[8] A. G. Anderson Jr., J. A. Nelson, and J. J. Tazuma *J. Amer. Chem. Soc.* **75**, 4980 (1953).
[9] D. Ginsburg and R. Pappo *J. Chem. Soc.* 938 (1951).
[10] C. D. Gutsche *J. Amer. Chem. Soc.* **70**, 4150 (1948).
[11] C. D. Gutsche *J. Amer. Chem. Soc.* **73**, 786 (1951).

shows that XV cannot be coplanar, so that the formation of this derivative is another case in which a tropone gives a ketonic derivative. The ultra-violet absorption supports this formulation and is analogous to spectral data obtained in related systems.[12]



XIV



XV

EXPERIMENTAL*

1-Benzoylcyclopentene was prepared by the published procedure,[13] b.p 117–125°/1 mm.

Michael condensation with dibenzyl malonate was carried out as reported,[5] using 1-benzoylcyclopentene (58 g), dibenzyl malonate (116 g), and potassium *tert.*-butoxide [from potassium (1·35 g) and *tert.*-butanol (21·5 ml)]. After 3 hr at 60° with occasional shaking and standing overnight at room temperature, acetic acid (3 ml) and ethyl acetate (480 ml) were added. Apparently because of traces of sulphur compounds from the preparation of the acceptor, the mixture must be refluxed for 4 hr over Raney nickel (20–30 g). After filtration, hydrogenolysis is effected, using palladised charcoal (10%; 10·6 g) at an initial pressure of 60 lb/sq. in. and 55°. When 2 moles of hydrogen had been absorbed, the catalyst was removed by filtration and the solution extracted with 10% aqueous sodium carbonate. After the usual workup,[4] *benzoylcyclopentane* (35 g) formed by reduction of unreacted starting material, b.p. 92–97°/1·5 mm;[14] n_D^{20} 1·5426[15] and trans-*2-benzoylcyclopentylmalonic acid* (*c.* 40 g), m.p. 144–145° (from carbon tetrachloride), were obtained, Lit. m.p. 144–145°.[5] The acidic fraction also contains the half benzyl ester of the malonic acid (*c.* 17 g).

Since reduction of 1-benzoylcyclopentene, at the expense of hydrogenolysis of the benzyloxy groups, could not be avoided, this method of debenzylation was abandoned in favour of hydrogen bromide in glacial acetic acid.[6, 16]

For the scale described above, a solution of hydrogen bromide in acetic acid (33%; 300 ml) is added to the reaction mixture. After standing overnight at room temperature, only one benzyl group is removed, since decarboxylation of the acidic material thus obtained affords trans-*benzyl 2-benzoylcyclopentyl acetate* identical with material described below. However, refluxing the mixture for 4 hr affords the free *malonic acid*. By this method, of course, unreacted 1-benzoylcyclopentene can be recovered.

Decarboxylation of hydrogenolysis product was effected by heating at 180–190° for 20 min. The trans-*2-benzoylcyclopentylacetic acid* had b.p. 133–138°/0·5 mm and formed colourless plates, m.p. 66–67° (from carbon tetrachloride) (Found: C, 72·09; H, 7·17. $C_{14}H_{16}O_3$ requires C, 72·39; H, 6·94%). Infra-red absorption (chloroform): 1677 cm^{-1} (acetophenone type C=O); 1711 cm^{-1} (C=O of saturated acid).

* M.p.'s. and b.p.'s are uncorrected.

[12] D. Ginsburg and W. J. Rosenfelder *Tetrahedron* **1**, (1957).
[13] R. C. Fuson, R. Johnson, and W. Cole *J. Amer. Chem. Soc.* **60**, 1594 (1938).
[14] D. Y. Curtin and S. Schmukler *J. Amer. Chem. Soc.* **77**, 1105 (1955).
[15] F. S. Bridson-Jones and G. D. Buckley *J. Chem. Soc.* 3015 (1951).
[16] Y. Klibansky and D. Ginsburg *J. Chem. Soc.* 1293 (1957).

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In addition a neutral product was obtained by decarboxylation of the half ester trans-*benzyl 2-benzoylcyclopentyl acetate*, b.p. 190–200°/1·4 mm (Found: C, 73·50; H, 7·90. $C_{21}H_{22}O_3$ requires C, 73·82; H, 7·74%). Infra-red absorption (chloroform): 1677 cm^{-1} (weak band, acetophenone C=O); 1731 cm^{-1} (C=O of saturated ester); 1170, 1160 cm^{-1} (pseudo-ester in ether region).

The ester gave a yellow-orange 2:4-*dinitrophenylhydrazone*, m.p. 124–125° (from ethanol) (Found: C, 64·70; H, 4·96; N, 11·09. $C_{27}H_{26}O_6N_4$ requires C, 64·53; H, 5·22; N, 11·15%).

Refluxing the ester (3 g) with ethanolic (30 ml) potassium hydroxide (10 g) for 2 hr affords the acetic acid (2·1 g), m.p. 66–67°. The overall yield of the acetic acid from the Michael condensation is therefore 52%.

δ-Lactone (VI)

On occasion, decarboxylation of the acidic product of hydrogenolysis afforded a *neutral compound* which formed colourless leaves, m.p. 109° (from ether). It gave no ketonic derivatives. Infra-red absorption (chloroform): 1746 cm^{-1} (δ-lactone) (Found: C, 77·58; H, 7·46. $C_{14}H_{16}O_2$ requires C, 77·75; H, 7·42%). The compound was soluble in 10% sodium hydroxide solution after 30 min boiling, but was recovered unchanged upon acidification of the alkaline solution.

Diol (VII)

A mixture of the δ-lactone (1 g), lithium aluminium hydride (200 mg), and dry ether (200 ml) was heated on the steam bath for 2 hr. After the usual workup, using alkali to decompose the reaction mixture, evaporation of the ether afforded glistening colourless leaves of the *diol*, m.p. 120° (from ether) (Found: C, 76·12; H, 9·20; Zerewitinoff, 1·97. $C_{14}H_{20}O_2$ requires C, 76·32; H, 9·15%; Zerewitinoff, 2·0).

Sodium borohydride reduction of trans-2-*benzoylcyclopentylacetic acid*

Sodium borohydride (0·5 g) was added portionwise to a solution of the keto-acid (0·5 g) in methanol (10 ml) and the mixture was permitted to stand overnight. After the usual workup, the *hydroxy-acid* (*V*) was obtained, m.p. 108·5° (from carbon tetrachloride) (Found: C, 71·78; H, 7·80; Zerewitinoff, 2·01. $C_{14}H_{18}O_3$ requires C, 71·77; H, 7·74%; Zerewitinoff, 2·0). The same hydroxy-acid was obtained by reduction of the keto-benzyl ester with sodium borohydride. The hydroxy-ester thus obtained exhibited bands at 1731 cm^{-1} (C=O of saturated ester) and 3460 cm^{-1} (secondary OH) in its infra-red spectrum. Alkaline hydrolysis afforded the hydroxy-acid described above.

γ-Lactone (VIII)

(a) The above hydroxy-acid was refluxed in toluene in the presence of naphthalene-β-sulphonic acid; the theoretical quantity of water expected was collected in an azeotropic collector. After removal of the catalyst and solvent, the *γ-lactone* was obtained as a colourless oil which showed a band at 1765 cm^{-1} (*γ-lactone*) in its infra-red spectrum. (b) A product completely identical in infra-red spectrum with that obtained above was formed by heating the hydroxy-acid on the steam bath with 50%

sulphuric acid for 1 hr. (c) The δ-lactone (50 mg) was refluxed with sulphuric acid (50%; 1 ml) in acetic acid (3 ml) for 48 hr. After dilution with water and ether extraction, drying (sodium sulphate), and removal of the ether, the colourless *γ-lactone* was obtained, again identical in infra-red spectrum with the products described in (a) or (b) above.

trans-2-*Benzylcyclopentylacetic acid*

2-Benzoylcyclopentylacetic acid (25 g) was reduced by the Huang-Minlon procedure,[17] using potassium hydroxide (20·4 g), hydrazine hydrate (85%; 12·4 ml) in diethylene glycol. The *acid* product (22·3 g; 95%) had b.p. 160–166°/0·5 mm, m.p. 53–54° (from light petroleum) (Found: C, 77·33; H, 8·53. $C_{14}H_{18}O_2$ requires C, 77·03; H, 8·31%).

trans-7-*Oxo*-1:2:3:4:7:8:9:10-*octahydro*-5:6-*benzazulene*

(a) *Intramolecular Friedel-Crafts cyclisation.* 2-Benzylcyclopentylacetic acid (7·6 g) was converted into its acid chloride in the usual way by using thionyl chloride (15 ml) in dry benzene (40 ml). After refluxing for 4 hr the excess thionyl chloride and the benzene were removed at the water-pump. The acid chloride was dissolved in dry carbon disulphide (40 ml) and aluminium chloride (4·75 g; 1·1 mole) was added portionwise with cooling. The mixture was then refluxed for 2 hr and allowed to stand overnight. After the usual workup, uncyclised acid (2·9 g) was recovered and the neutral fraction was distilled. The desired *ketone* had b.p. 120–123°/0·3 mm (4·5 g; 65%) and crystallised spontaneously after distillation, m.p. 56° (from methanol); Lit.[7] m.p. 56°. Infra-red absorption (chloroform): 1675 cm^{-1} (C=O). Ultra-violet absorption: $\lambda\lambda_{max}^{EtOH}$ 2450, 2810 Å. $\varepsilon\varepsilon_{max}$ 6300, 1160.

The 2:4-*dinitrophenylhydrazone* formed orange rhombic plates, m.p. 194–196° (from ethanol-ethyl acetate); Lit. m.p. 184–185°, 169–170°, respectively[5, 7] (Found: C, 63·50; H, 5·32. Calc. for $C_{20}H_{20}O_4N_4$: C, 63·15; H, 5·30%). Ultra-violet absorption: λ_{max}^{chf} 3690 Å; ε_{max} 25,200.

The *oxime* was prepared by the pyridine method, m.p. 153·5–154·5° (from methanol) (Found: C, 78·38; H, 8·34; N, 6·37. $C_{14}H_{17}ON$ requires C, 78·10; H, 7·96; N, 6·51%).

The semicarbazone had m.p. 210–211° (from ethanol) (Found: N, 16·30. $C_{15}H_{19}ON_3$ requires N, 16·33%). Ultra-violet absorption: λ_{max}^{chf} 2550 Å; ε_{max} 9250.

(b) *Polyphosphoric acid cyclisation.* A mixture of the acid (4 g) and polyphosphoric acid (80 g; Victor Chemical Co.) was heated on the steam bath with vigorous mechanical stirring for 2 hr. After cooling and pouring on ice, the organic material was extracted with ether. The ether solution was washed with 5% sodium hydroxide to remove uncyclised acid (0·1 g). Removal of the ether afforded the ketone, identical with that described in (a) (3·85 g; 96%).

trans-7-*Hydroxy*-1:2:3:4:7:8:9:10-*octahydro*-5:6-*benzazulene*

The above ketone (10 g) was reduced in the usual way with sodium borohydride (7·5 g) in methanol (125 ml). The *alcohol*, m.p. 128° (from light petroleum) was obtained in quantitative yield; Lit. m.p. 128°.[7] Infra-red absorption (chloroform): 3460 cm^{-1} (secondary OH).

[17] Huang-Minlon *J. Amer. Chem. Soc.* **68**, 2487 (1946).

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trans-1:2:3:4:9:10-*Hexahydro*-5:6-*benzazulene*

A mixture of the above alcohol (5 g), dry toluene (100 ml), and naphthalene-β-sulphonic acid monohydrate (0·5 g) was refluxed. The theoretical amount of water expected (0·45 ml) was obtained in the azeotropic collector during 1 hr. After the usual workup, the *olefin* is obtained, m.p. 33–35° (without recrystallisation). Lit.[7] m.p. 29–35°. Ultra-violet absorption: λ_{max}^{EtOH} 2600 Å; ε_{max} 10,500.

Aromatization with N-*bromosuccinimide*

A mixture of 1:2:3:4:9:10-hexahydro-5:6-benzazulene (4 g), dry carbon tetrachloride (70 ml) and powdered *N*-bromosuccinimide (4·25 g; 1·1 mole) was refluxed for 2 hr. After cooling, the succinimide floating on top of the solvent was filtered and the solvent was removed from the filtrate at the water pump. Some hydrogen bromide evolution was observed, 2:6-lutidine (70 ml) was added to the residue, and the mixture was refluxed for 4 hr. Most of the solvent was removed at the water pump. Water was added to the residue and the mixture was extracted with ether. The ether extract was washed with dilute hydrochloric acid and the ether solution was dried (sodium sulphate) and the solvent was removed. The residue was practically all recovered starting material together with a small amount of highly-coloured material which could not be isolated.

The bromination was therefore repeated, but without the lutidine treatment. The bromination residue was taken up in light petroleum and chromatographed on alumina (Merck, acid-washed). The first and major fraction obtained (3·8 g) was starting material. The second fraction was a hydro-5:6-benzazulene, m.p. 188–189° (from light petroleum), whose exact structure could not be determined because it was formed in very small quantity. Its ultra-violet absorption did not show more extended conjugation than was present in the starting material. The third fraction was a colourless dibromohydro-5:6-benzazulene, m.p. 72° (from pentane) (Found: C, 48·89; H, 4·58; Br, 46·65. $C_{14}H_{14}Br_2$ requires C, 49·15; H, 4·12; Br, 46·73%).

A deep-purple product (0·2 g) was then obtained in needles, m.p. >360°; the compound decomposes during heating. This product was purified by formation of its complex with trinitrobenzene, m.p. 118–121°. The complex decomposed on alumina and afforded long deep-purple needles (Found: C, 50·8; H, 2·3; Br, 48·7. $C_{14}H_8Br_2$ requires C, 50·0; H, 2·4; Br, 47·6%). This product is formulated as 1(?):3(?)-*dibromo*-5:6-*benzazulene*. Ultra-violet absorption: $\lambda\lambda_{max}^{iso\text{-}octane}$ 2580, 3080, 3620, 3800, 4000, 5850 Å; $\varepsilon\varepsilon_{max}$ 25,850, 64,850, 6850, 7450, 7350, 1000.

The final product isolated (0·3 g) formed short green-violet needles, m.p. 224–226° (from dioxane) is a *tetrabromo*-5:6-*benzazulene* (Found: C, 35·0; H, 1·4; Br, 63·5. $C_{14}H_6Br_4$ requires C, 34·0; H, 1·2; Br, 64·8%). Ultra-violet absorption: $\lambda\lambda_{max}^{iso\text{-}octane}$ 2540, 3175–3240, 3570, 3750–3770, 3940, 4140–4150, 5050–5100, 5500, 5600, 5750, 5850 Å; $\varepsilon\varepsilon_{max}$ 22,000, 70,700, 5150, 6200, 5750, 4100, 575, 850, 825, 900, 875. These values for the two bromo-compounds may be compared with those obtained for 5:6-benzazulene, the parent hydrocarbon whose ultra-violet absorption[3] follows: $\lambda\lambda_{max}^{iso\text{-}octane}$ 2500, 2800, 3530, 3700, 5500–5700, 5820 Å; $\varepsilon\varepsilon_{max}$ 18,000, 56,000, 4000, 2950, strong, strong. As expected, the bromo-derivatives exhibit a bathochromic shift in their spectra.

1-*Benzoylcycloheptane* was prepared by the published procedure,[5] b.p. 155°/8 mm.

trans-2-*Benzoylcycloheptylmalonic acid* was prepared in exact analogy to the

cyclopentyl analogue described above, m.p. 169–170° (from carbon tetrachloride). Decarboxylation of the hydrogenolysis reaction mixture, as above, gave 2-*benzoylcycloheptylacetic acid*, b.p. 190–194°/0·2 mm, m.p. 95–96° (from heptane) (Found: C, 73·90; H, 7·75. $C_{16}H_{20}O_3$ requires C, 73·82; H, 7·74%). It was accompanied by its *benzyl ester*, b.p. 145–155°/0·2 mm, which exhibited in its infra-red spectrum weak bands at 1677 cm^{-1} and 1731 cm^{-1} and strong bands at 1170 and 1160 cm^{-1}, indicating the presence of a large proportion of pseudo-ester. The ester was saponified to the free acid by boiling with hydrogen bromide in acetic acid for 2 hr. The overall yield of the acetic acid from the Michael condensation was thus 53%.

trans-2-*Benzylcycloheptylacetic acid* was prepared in nearly quantitative yield in analogy to the cyclopentyl analogue from the keto-acid (25 g), potassium hydroxide (18·6 g), hydrazine (100%; 11·5 ml), and diethylene glycol (133 ml). The *acid* had b.p. 166–169°/0·5 mm and m.p. 63·5–64·5° (from pentane) (Found: C, 78·10; H, 9·00. $C_{16}H_{22}O_2$ requires C, 78·01; H, 9·00%).

trans-4-*Oxo*-1:4:5:6:7:8:9:10:11:12-*decahydro*-2:3-*benzheptalene*

The ketone was prepared by intramolecular cyclisation of the acid chloride with aluminium chloride in carbon disulphide (see above). The acid (17·8 g) gave a small amount of recovered uncyclised acid (3·7 g) and the oily *ketone* (13·3 g, 81%), b.p. 152–160°/0·6 mm. Infra-red absorption (chloroform): 1668 cm^{-1} (C=O). Ultra-violet absorption: $\lambda\lambda_{max}^{EtOH}$ 2470–2490, 2870–2910 Å; $\varepsilon\varepsilon_{max}$ 9280, 1750.

The ketone was also prepared quantitatively in analogy to its five-membered homologue by cyclization with polyphosphoric acid. It was characterised as the orange 2:4-*dinitrophenylhydrazone*, m.p. 247–248° (from ethanol-ethyl acetate) (Found: C, 64·90; H, 6·07; N, 13·57. $C_{22}H_{24}O_4N_4$ requires C, 64·69; H, 5·92; N, 13·72%). Ultra-violet absorption: λ_{max}^{chf} 3770 Å; ε_{max} 25,500.

The *oxime* was prepared in pyridine and formed colourless crystals, m.p. 155–156° (from methanol) (Found: C, 78·85; H, 8·38; N, 5·67. $C_{16}H_{21}ON$ requires C, 78·97; H, 8·70; N, 5·76%).

The colourless *semicarbazone* had m.p. 202–203° (from ethanol) (Found: C, 71·07; H, 7·88; N, 14·83. $C_{17}H_{23}ON_3$ requires C, 71·54; H, 8·12; N, 14·73%). Ultra-violet absorption: λ_{max}^{chf} 2580–2680 Å; ε_{max} 19,400.

trans-4-*Hydroxy*-1:4:5:6:7:8:9:10:11:12-*decahydro*-2:3-*benzheptalene*.

The ketone (10 g) was reduced in methanol (100 ml) with sodium borohydride (6·5 g) in the usual way. The *alcohol* was obtained in quantitative yield, m.p. 108–109° (from light petroleum) (Found: C, 83·20; H, 9·70. $C_{16}H_{22}O$ requires C, 83·42; H, 9·63%).

trans-1:6:7:8:9:10:11:12-*Octahydro*-2:3-*benzheptalene*.

The alcohol (6·6 g) in toluene (120 ml) containing naphthalene-β-sulphonic acid monohydrate (0·6 g) afforded after 1 hr of reflux the expected amount of water (0·5 ml). After the usual workup the *olefin* was obtained as an oil, b.p. 122–126°/0·2 mm; $n_D^{21.5}$ 1·5794. Ultra-violet absorption: λ_{max}^{EtOH} 2540 Å; ε_{max} 14,860.

Bromination experiments

(a) The olefin (2·9 g) was refluxed in dry carbon tetrachloride (60 ml) with powdered *N*-bromosuccinimide (2·47 g; 1·1 mole) for 45 min. At this time the reaction

was over and hydrogen bromide could be observed. After the usual workup, the reaction mixture was distilled, b.p. 130°/0·3 mm. The ultra-violet spectrum showed this was mainly starting material, but the analysis showed the material contained *c.* 20% bromine. Chromatography of the product before or after dehydrobromination did not permit isolation of pure material. Use of excess NBS in brominations with the hope that completely aromatised material could be isolated, failed.

(b) Bromination of 4-*oxo*-1:4:5:6:7:8:9:10:11:12-*decahydro*-2:3-*benzheptalene*—A mixture of the ketone (4·1 g), dry carbon tetrachloride (50 ml) and NBS (3·56 g; 1 mole) was refluxed. Reaction was complete after 1 hr. Dehydrobromination was effected with 2:6-lutidine. After the usual workup, distillation afforded the starting material (3·3 g) and a fraction of a *ketone* b.p. 193°/0·3 mm (0·5 g). This crystallised after standing, m.p. 86–88° (from light petroleum). Infra-red absorption (chloroform): 1626, 1578 cm^{-1} (tropone C=O). Ultra-violet absorption: $\lambda\lambda_{max}^{EtOH}$ 2300, 3200, 3500 Å; $\varepsilon\varepsilon_{max}$ 31,000, 6400, 5800. The ketone gave a 2:4-*dinitrophenylhydrazone* which formed short brownish-crimson needles, m.p. 242·5–243° (from ethanol-ethyl acetate) (Found: C, 65·43; H, 4·74; N, 13·72. $C_{22}H_{20}O_4N_4$ requires C, 65·40; H, 4·95; N, 13·86%). Ultra-violet absorption: λ_{max}^{chf} 4000 Å; ε_{max} 26,700.

trans-3-*Oxo*-2-*phenylcycloheptylacetic acid* was prepared by the published procedure,[4] m.p. 115° (from benzene). Lit.[4] m.p. 115°. trans-2-*Phenylcycloheptylacetic acid* was prepared from the keto-acid (8 g) by the Huang-Minlon method,[17] using potassium hydroxide (6·2 g), hydrazine (3·8 ml; 100%) in diethylene glycol (45 ml), in almost quantitative yield, as an oil which solidified upon trituration with light petroleum, m.p. 68° (from hexane). Lit.[4] m.p. 68–69°. This procedure is better than the published preparation by Clemmensen reduction.[4]

trans-3-*Oxo*-2-*phenylcycloheptylpropionic acid*

A mixture of the acetic acid (13 g), dry benzene (50 ml), and thionyl chloride (80 ml) was refrigerated for 48 hr.[18] The excess solvents were removed in a high vacuum. Dry benzene was again added and removed in a high vacuum to help remove traces of thionyl chloride. The acid chloride was then dissolved in dry benzene (10 ml) and dry ether (10 ml) and the solution was added to an ether solution containing diazomethane (14·5 g) at 0°. After 2 hr the solvents and excess of diazomethane were removed by distillation and the residue was dissolved in hot absolute ethanol (100 ml) and treated portionwise with dry freshly precipitated silver oxide (10 g). The mixture was refluxed for 3 hr while nitrogen was evolved. Charcoal (3 g) was added and boiling was continued for 15 min. The mixture was then cooled and filtered. Saponification of the ester thus obtained was effected by adding potassium hydroxide (*c.* 10 g) to the solution and refluxing for 4 hr. After the usual workup, acidic material was isolated (9·9 g). Separation between the propionic acid and unreacted acetic acid was accomplished by treating the mixture of acids with anhydrous hydrogen fluoride (*c.* 200 ml). The acetic acid was quantitatively cyclised and gave *trans*-5:11-dioxo-6:6a:7:8:9:10:11:11a-octahydro-5H-cyclohepta[a]naphthalene, m.p. 106° (from light petroleum).[4] The *propionic acid* remained unchanged and was obtained as a viscous oil (6·7 g; 50%) which crystallised on standing, m.p. 116–118° (from light petroleum) (Found: C, 73·40; H, 7·50. $C_{16}H_{20}O_3$ requires C, 73·82; H, 7·74%).

[18] D. Ginsburg and R. Pappo *J. Chem. Soc.* 1524 (1953).

trans-2-*Phenylcycloheptylpropionic acid*

As there was no possibility, in this case, of obtaining an enol lactone during the treatment with thionyl chloride, the corresponding acetic acid was converted to the acid chloride by refluxing with thionyl chloride in dry benzene. The Arndt-Eistert reaction and workup were carried out exactly as just described for the keto-acid. In this case, hydrogen fluoride treatment caused conversion of unreacted acetic acid to *trans*-5-oxo-6:6a:7:8:9:10:11:11a-octahydro-5H-cyclohepta[a]naphthalene, m.p. 60–61°, whilst the *propionic acid* was unchanged in this treatment and was obtained as a yellow oil, b.p. 152–158°/0·5 mm (55% yield) (Found: neut. equiv., 250. $C_{16}H_{22}O_2$ requires 246). The *methyl ester* prepared by diazomethane esterification of the acid was an oil, b.p. 167°/2 mm.

trans-3-*Oxo*-3:4:5:6:7:8:9:10:11:12-*decahydro*-1:2-*benzheptalene*

The propionic acid just described (2·5 g) was converted through the acid chloride exactly as described for the five-membered homologue (see above) to the ketone (1·05 g). A part of the propionic acid was recovered (0·7 g). The same *ketone* was obtained in nearly quantitative yield by cyclisation with polyphosphoric acid in the usual way. It was an oil, b.p. 190°/0·4 mm. Infra-red absorption (chloroform): 1669 cm^{-1} (C=O). Ultra-violet absorption: $\lambda\lambda_{max}^{EtOH}$ 2500, 2770–2860 Å; $\varepsilon\varepsilon_{max}$ 9500, 1700.

It was characterised as the colourless *semicarbazone*, m.p. 204° (from ethanol) (Found: N, 14·60. $C_{17}H_{23}ON_3$ requires N, 14·73%). Ultra-violet absorption: λ_{max}^{chf} 2580–2600 Å; ε_{max} 19,400. Gutsche[11] reports m.p. 239–240° for the isomeric semicarbazone, which must therefore be the derivative of the *cis*-isomer.

The yellow-orange 2:4-*dinitrophenylhydrazone* had m.p. 209–211° (from ethanol) (Found: N, 13·40. $C_{22}H_{24}O_4N_4$ requires N, 13·72%). Ultra-violet absorption: λ_{max}^{chf} 3650 Å; ε_{max} 24,000.

trans-3:10-*Dioxo*-3:4:5:6:7:8:9:10:11:12-*decahydro*-1:2-*benzheptalene*

The keto-propionic acid was converted into the diketone by intramolecular cyclisation of its acid chloride in the usual way. The *diketone* was obtained as an oil which after purification by chromatography on alumina solidified upon refrigeration, but was liquid at room temperature (Found: C, 79·10; H, 7·70. $C_{16}H_{18}O_2$ requires C, 79·31; H, 7·49%). Infra-red absorption (chloroform): 1705 cm^{-1} (alicyclic C=O); 1669 cm^{-1} (C=O adjacent to aromatic nucleus). Ultra-violet absorption: $\lambda\lambda_{max}^{EtOH}$ 2460, 2840 Å, $\varepsilon\varepsilon_{max}$ 8900, 3150.

The orange-brown *mono*-2:4-*dinitrophenylhydrazone* had m.p. 197–199° (from dioxane) (Found: C, 62·70; H, 5·40. $C_{22}H_{22}O_5N_4$ requires C, 62·55; H, 5·25%). The infra-red spectrum showed that the alicyclic carbonyl group was free (band at 1705 cm^{-1}). Ultra-violet absorption: λ_{max}^{chf} 3630 Å; ε_{max} 28,500.

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Tetrahedron, 1957, Vol. 1, pp. 19–21. Pergamon Press Ltd., London

ALICYCLIC STUDIES—XII*

AN ALICYCLIC SYNTHESIS OF 2:3,6:7-DIBENZOTROPONE

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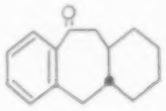
(*Received* 31 *December* 1956)

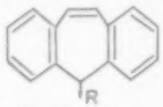
Abstract—*trans*-2-Benzylcyclohexylacetic acid was cyclised with polyphosphoric acid to give *trans*-2:3-benzo-5:6-cyclohexanocycloheptanone. Reduction to the corresponding alcohol followed by dehydration and dehydrogenation afforded 2:3,6:7-dibenzocyclohepta-3:4:6-triene, which was oxidized with selenium dioxide to 2:3,6:7-dibenzotropone.

THE reported preparation of *trans*-2-benzylcyclohexylacetic acid[1] has been improved experimentally, and cyclisation by means of polyphosphoric acid afforded a quantitative yield of *trans*-2:3-benzo-5:6-cyclohexanocycloheptanone (I). This ketone was reduced with sodium borohydride to the corresponding alcohol and the latter was dehydrated to the olefin (II) by naphthalene-β-sulphonic acid. Dehydrogenation by



I

II



IIIa R=H$_2$
b R=O

30% palladised charcoal in the absence of solvent afforded 2:3,6:7-dibenzocyclohepta-2:4:6-triene (IIIa) identical with the Huang-Minlon reduction product of an authentic specimen of 2:3,6:7-dibenzotropone.[2] Attempts by various investigators to oxidise the triene (IIIa) to the ketone (IIIb) were unsuccessful.[3] Under various conditions (see experimental section), 9:10-anthraquinone is indeed obtained.[3] However, the oxidation to 2:3,6:7-dibenzotropone (IIIb) was effected in high yield through the use of freshly sublimed selenium dioxide in dry dioxane in a sealed tube at elevated temperature.

EXPERIMENTAL†

1-*Benzoylcyclohexene* was prepared by the published procedure,[4] b.p. 147°/8 mm.

2-*Benzoylcyclohexylmalonic acid* was prepared by the published procedure, m.p. 190–191° (from carbon tetrachloride), as reported.[1] Decarboxylation yielded a mixture of 2-benzoylcyclohexylacetic acid and its benzyl ester, which could be saponified to the acid (total yield, 50%). The *acid* had m.p. 103–104°, as reported.[1] Infra-red absorption (chloroform): 1677 cm^{-1} (acetophenone C=O); 1711 cm^{-1} (C=O of saturated acid).

* Part XI, Amiel and Ginsburg *Tetrahedron* **1** (1957).
† Melting-points are uncorrected.
[1] D. Ginsburg *J. Chem. Soc.* 2361 (1954).
[2] E. D. Bergmann and D. Ginsburg *Bull. Res. Council Israel* **1**, No. 3, 120 (1951).
E. D. Bergmann *et al. Bull. Soc. Chim. France* **18**, 684 (1951).
[3] W. Treibs and H. J. Klinkhammer *Chem. Ber.* **84**, 671 (1951); **83**, 367 (1950).
[4] R. E. Christ and R. C. Fuson *J. Amer. Chem. Soc.* **59**, 893 (1937).

2-Benzylcyclohexylacetic acid was prepared by Huang-Minlon reduction[5] of the keto-acid (16 g), using potassium hydroxide (12·4 g), hydrazine (100%; 7·6 ml) in diethylene glycol (90 ml). The acid (15·1 g) had b.p. 158–163°/0·5 mm, m.p. 74–75° (from light petroleum), as described previously.[1]

trans-2:3-*Benzo*-5:6-*cyclohexanocycloheptanone*

(a) *Intramolecular Friedel-Crafts cyclisation.* 2-Benzylcyclohexylacetic acid (17·8 g) was refluxed with thionyl chloride (45 ml) in dry benzene (100 ml) for 4 hr. After removal of benzene and excess thionyl chloride at the water-pump, dry carbon disulphide (100 ml), and anhydrous aluminium chloride (11·4 g) were added portionwise, and finally the mixture was boiled for 2 hr. After the usual workup, uncyclised acid (3·0 g) was recovered and the *ketone* was obtained by distillation (13·2 g; 83%), b.p. 142–146°/0·5 mm. Infra-red absorption (chloroform): 1671 cm^{-1} (C=O). Ultraviolet absorption: $\lambda\lambda_{max}^{EtOH}$ 2460–2470, 2870 Å; $\varepsilon\varepsilon_{max}$ 7750, 1390.

The ketone was characterised as the yellow-orange 2:4-*dinitrophenylhydrazone* which formed prisms, m.p. 235·5–236·5° (from ethanol-ethyl acetate) (Found: C, 64·07; H, 5·61; N, 14·13. $C_{21}H_{22}O_4N_4$ requires C, 63·94; H, 5·62; N, 14·21%). Ultra-violet absorption: λ_{max}^{chf} 3710 Å; ε_{max} 29,250.

The colourless *oxime* was formed in pyridine, m.p. 143·5–144·5° (from methanol) (Found: C, 78·42; H, 8·27; N, 6·12. C_{15}, $H_{19}ON$ requires C, 78·56; H, 8·35; N, 6·11%).

The colourless *semicarbazone* had m.p. 205° (from ethanol). Lit.[6] m.p. 205°. Ultraviolet absorption: λ_{max}^{chf} 2580–2640 Å; ε_{max} 16,650.

(b) *Polyphosphoric acid cyclisation.* The acid (4 g) was stirred on the steam bath for 2 hr with polyphosphoric acid (80 g; Victor Chemical Co.). After the usual workup the same ketone as described in (a) was obtained in quantitative yield.

trans-2:3-*Benzo*-5:6-*cyclohexanocycloheptanol*

The ketone (10·7 g; 0·05 mole) was dissolved in methanol (125 g) and sodium borohydride (7·5 g; 0·2 mole) was added portionwise. After standing overnight, the mixture was worked up in the usual way and the *alcohol* was obtained in quantitative yield (10·7 g), m.p. 128–129° (from light petroleum) (Found: C, 83·20; H, 9·20. $C_{15}H_{20}O$ requires C, 83·24; H, 9·32%).

2:3:12:13:14:15-*Hexahydro*-2:3,6:7-*dibenzocyclohepta*-2:4-*diene*

The above alcohol (8·24 g) was dehydrated by boiling in toluene (125 ml) in the presence of naphthalene-β-sulphonic acid monohydrate (0·5 g). The theoretical quantity of water (0·7 ml) was obtained in the azeotropic collector during 1 hr. After the usual workup, the *olefin* was obtained as an oil, b.p. 106–108°/0·2 mm, which crystallised on cooling to form colourless needles, m.p. 37–38° (from methanol) (Found: C, 90·54; H, 9·00. $C_{15}H_{18}$ requires C, 90·91; H, 9·09%). Ultra-violet absorption: λ_{max}^{EtOH} 2580 Å; ε_{max} 14,500.

2:3,6:7-*Dibenzocyclohepta*-2:4:6-*triene*

Refluxing the above olefin with an equal weight of 30% palladised charcoal in *p*-cymene for 6 hr under nitrogen afforded unreacted starting material.

[5] Huang-Minlon *J. Amer. Chem. Soc.* **68**, 2487 (1946).
[6] J. Colonge and J. Sibeud *Compt. Rend.* **234**, 530 (1952).

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A mixture of the olefin (1·5 g) and palladised charcoal (30%; 1·5 g) was heated under nitrogen for 5 hr at 300–320°. After cooling, benzene was added and the catalyst filtered. The catalyst was boiled several times with fresh portions of benzene, and filtered. The combined benzene extracts afforded after removal of the solvent, the *cycloheptatriene* (1·3 g), m.p. 130–131°; lit.[3] m.p. 130–131°. An authentic specimen of this compound was prepared by Huang-Minlon reduction[5] of 2:3,6:7-dibenzotropone, which was available from another synthetic route.[2] The m.p. of the triene thus obtained (130–131°) was undepressed upon admixture with the above triene. Ultra-violet absorption; $\lambda\lambda_{max}^{heptane}$ 2530, 2860 Å; $\varepsilon\varepsilon_{max}$ 5400, 13,650.

Attempted oxidations of triene to 2:3,6:7-*dibenzotropone*

(a) In analogy to fluorene oxidation,[7] to a boiling solution of the triene (0·5 g) in glacial acetic acid (1·2 ml) was added dropwise a solution of sodium dichromate (1·7 g) in glacial acetic acid (2·5 ml) and water (0·6 ml). Refluxing was continued for 2 hr; the orange solution turned green. After pouring into ice-water (20 ml) the mixture was allowed to stand for 2 hr and was then filtered. The solid had m.p. 262–270°, which was raised to 278° after recrystallisation from benzene. Sublimation afforded 9:10-*anthraquinone*, m.p. 283°, undepressed by an authentic specimen.

Heating the above mixture on the steam bath for only 1 hr afforded the quinone, while allowing it to stand at room temperature for 24 hr gave unreacted starting material even when a little benzene was added to produce a completely homogeneous solution.

(b) Attempted oxidation in a two-phase acetic acid-benzene system[8] afforded unreacted starting material.

(c) A mixture of the triene (0·42 g), dry dioxane (7·5 ml), and selenous acid (0·33 g; 1·1 mole) was refluxed for 36 hr. After removal of selenium by filtration (*c.* 20% of the theoretical amount), sulphur dioxide was bubbled through the filtrate; red colloidal selenium was obtained and was coagulated by boiling. After filtration and evaporation of the dioxane, the residue was chromatographed on alumina (light petroleum). The starting material was largely recovered and *anthraquinone* (12 mg) was again isolated. The use of freshly sublimed selenium dioxide or higher-boiling solvents such as xylene or acetic anhydride did not lead to the desired product.

2:3,6:7-*Dibenzotropone* was finally obtained by heating, in a sealed tube, a mixture of the triene (0·5 g), dry dioxane (10 ml), and freshly sublimed selenium dioxide at 160° for 6 hr. After cooling, the black selenium was filtered (0·17 g; theory 0·21 g) and the dioxane was evaporated. The residue (0·55 g) had m.p. 88° after trituration with ether. It had m.p. 89° (from methanol), undepressed upon admixture with an authentic specimen, m.p. 89°. It gave an orange-red 2:4-*dinitrophenylhydrazone*, m.p. 258°. Lit.[9] m.p. 258°.

The same reaction mixture even after 48 hr boiling in an open vessel afforded mainly recovered starting material.

[7] E. H. Huntress, E. B. Hershberg and I. S. Cliff *J. Amer. Chem. Soc.* **53**, 2720 (1931).
[8] Y. Mazur, E. Koller, O. Jeger and L. Ruzicka *Helv. Chim. Acta* **35**, 181 (1952).
[9] E. D. Bergmann and D. Ginsburg *Chem. and Ind.* 45 (1954).

Tetrahedron, 1957, Vol. 1, pp. 22–27. Pergamon Press Ltd., London

THE SYNTHESIS OF 8-*ISO*PROGESTERONE AND 8-*ISO*TESTOSTERONE*

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(*Received* 4 *February* 1957)

Abstract—The multi-stage conversion of diosgenin into 8-*iso*progesterone and 8-*iso*testosterone is described. These isomers, differing from the natural sex hormones only in the configuration of the inaccessible C-8 center, have been shown to possess considerable hormonal activity.

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A PART of the steroid program under way in these laboratories is concerned with the synthesis of hormone analogs which differ from the natural steroids only in the orientation of an inaccessible center. It appeared of interest to determine the effect of such a subtle structural alteration upon the biological activity and in particular to observe whether hormone antagonists might be produced, since such compounds would be of considerable biological and therapeutic significance. Attention was first directed at C-8, since inversion of configuration of that carbon atom would result in a steroid in which either ring *B* or ring *C* would now have to assume a boat conformation in contrast to the conventional all-chair arrangement of the natural steroids.

An 8-step synthesis of diosgenin (I) into 3β-propionoxy-22*a*,25*a*,5α,8α-spirostan-11-one† (IIIb) via the key intermediate Δ^8-3β-propionoxy-22*a*,25*a*,5α-spirosten-11-one (IIb) has already been described,[1] and the only modification introduced in the present work was that all transformations were carried out with the corresponding 3β-acetates (IIa, IIIa). Modified Wolff-Kishner reduction[2] of the 11-ketone IIIa followed by acetylation led to 8-isotigogenin acetate (IV), which represented the starting material for all subsequent operations. Conventional side-chain degradation[3] provided Δ^{16}-3β-acetoxy-5α,8α-pregnen-20-one (V), and this was hydrogenated readily to the saturated 3β-acetoxy-20-ketone VIa.‡ Saponification to the free alcohol VIb and chromium trioxide oxidation furnished 5α,8α-pregnane-3,20-dione (VIc), in which only the 4,5-double bond had to be introduced in order to give the desired progesterone isomer.

This problem had already been solved earlier[4] in a synthesis of 11α-hydroxyprogesterone and involved application of the 2,4-dibromo-3-keto sodium iodide reaction[5] to a polybrominated§ derivative followed by dehalogenation. A similar

* For preliminary communications see ref. 10.

† For steroidal sapogenin nomenclature employed see C. Djerassi, T. T. Grossnickle, and L. B. High *J. Amer. Chem. Soc.* **78,** 3166, ref. 10 (1956).

‡ Evidence for the correct stereochemistry at C-17 was provided by the rotatory dispersion curve (ref. 11) which showed a typical, strongly positive Cotton-effect curve. 17α-20-Ketosteroids, on the other hand, are characterised by a negative Cotton-effect curve (C. Djerassi *Bull. Soc. Chim. France*, in press).

§ An excess of bromine has to be added, since the 20-keto group is also affected. The poor yield is probably due to the fact that a pure 2, 4-dibromo compound is not isolated and the crude product is used directly (see R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephenson, T. Walker, and B. M. Wilson *J. Chem. Soc.* 4356 (1956)).

[1] C. Djerassi, W. Frick, G. Rosenkranz, and F. Sondheimer *J. Amer. Chem. Soc.* **75,** 3496 (1953).
[2] D. H. R. Barton, A. A. J. Ives, and B. R. Thomas *J. Chem. Soc.* 2056 (1955).
[3] Cf. R. E. Marker *J. Amer. Chem. Soc.* **62,** 3350 (1940).
[4] O. Mancera, J. Romo, F. Sondheimer, G. Rosenkranz, and C. Djerassi *J. Org. Chem.* **17,** 1066 (1952).
[5] G. Rosenkranz, O. Mancera, J. Gatica, and C. Djerassi *J. Amer. Chem. Soc.* **72,** 4077 (1950).

reaction sequence with VIc without isolation of intermediate bromo and iodo derivatives led directly to crystalline 8-*iso*progesterone (VII).

In order to prepare a similar isomer in the male sex hormone series, the above-described Δ^{16}-20-ketone V was converted into the oxime and subjected directly to Beckmann rearrangement.[6] The resulting 3β-hydroxy-8α-androstan-17-one (VIIIa) was oxidized to 8α-androstane-3,17-dione (VIIIb), dibrominated (IX),[7] heated with sodium iodide[5] and reduced with chromous chloride to afford the desired Δ^4-8α-androstene-3,17-dione (X). In the natural (8β) series, Δ^4-androstene-3,17-dione can be reduced[8] by means of sodium borohydride in good yield directly to testosterone, and it is interesting to note that inversion at C-8 apparently changed the reactivity of the two carbonyl functions. Thus, sodium borohydride reduction of the 8α-isomer X led to a product which lacked ultra-violet absorption in the 240-mμ region (characteristic of the Δ^4-3-keto moiety) but still exhibited an infra-red band typical of a 5-membered ketone. Consequently, resort was taken to an alternate testosterone synthesis[9] which is predicated on the oxidizability of allylic alcohols, in contrast to saturated alcohols, by means of manganese dioxide. As was to be anticipated, treatment of Δ^4-8α-androstene-3,17-dione (X) with lithium aluminum hydride resulted in reduction of both carbonyl systems and oxidation of the total crude product (XI) with manganese dioxide afforded 8-*iso*testosterone (XII).

As reported already in our preliminary communications,[10] both 8-*iso*progesterone (VII) and 8-isotestosterone (XII) possess approximately one-third to one-half the biological activity of the parent hormones. It is interesting to note that the geometrical alteration accompanying inversion of the C-8 center does not affect to a marked extent the hormonal potency but does affect in a very striking manner the rotatory dispersion.[11] The latter results indicate that it is ring *B* rather than *C* which has assumed a boat conformation in these 8-*iso* steroids.

The synthesis of stereoisomers of 11-oxygenated steroid hormones is now under way.

EXPERIMENTAL

Δ^8-3β-*Acetoxy*-22*a*,25*a*,5α-*spirosten*-11-*one* (IIa). Δ^7-3β-Acetoxy-9α,11α-oxido-22*a*,25*a*,5α-spirosten[12] (34 g) was dissolved in 500 c.c. of benzene and the solution was concentrated to 400 c.c. Freshly distilled boron trifluoride etherate (10 c.c.) was added and the solution was kept at *c.*70° for 10 min. The product, isolated with benzene, was adsorbed on 750 g of alumina and elution with hexane-benzene (1:1) and benzene afforded 24 g of the Δ^8-11-ketone (IIa), m.p. 213–220°. An analytical sample was obtained from ether-hexane as needles, m.p. 226–229°, $[\alpha]_D + 52°$, λ_{max}^{EtOH} 254 mμ, log ϵ 3·97, $\lambda_{max}^{CHCl_3}$ 5.82 and 6·05 μ.

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74·01; H, 9·00. Found: C, 73·79; H, 8·93.

* Melting-points are uncorrected. Unless noted otherwise, all rotations were measured in chloroform solution. We are indebted to Mrs. Dolores Phillips for all spectral determinations and to Geller Laboratories (Hackensack, New Jersey) and Dr. A. Bernhardt (Mülheim, Germany) for the microanalyses.

[6] G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi *J. Org. Chem.* **21,** 520 (1956).

[7] Cf. C. Djerassi and C. R. Scholz *J. Org. Chem.* **13,** 697 (1948).

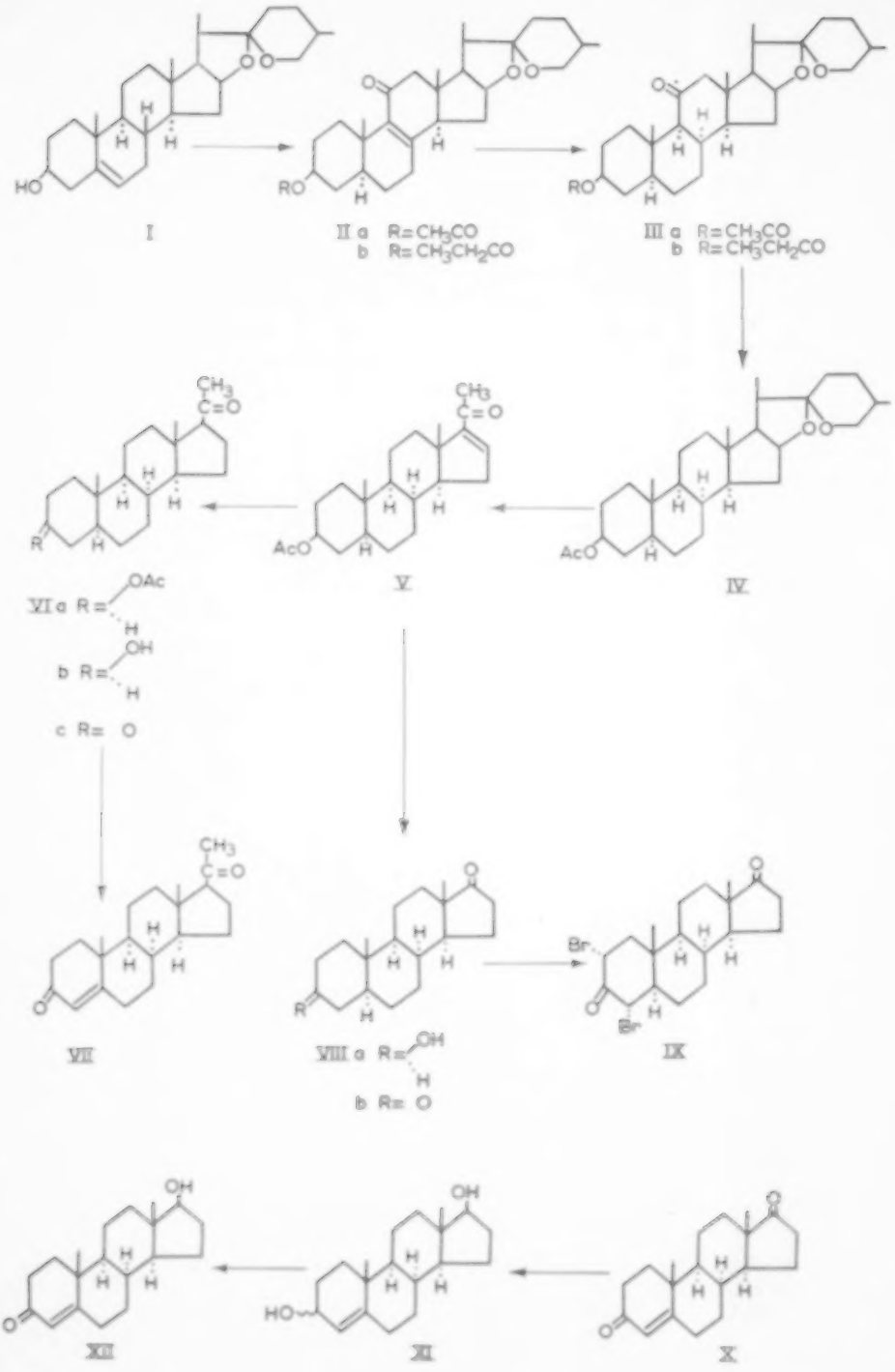
[8] J. K. Norymberski and G. F. Woods *J. Chem. Soc.* 3426 (1955).

[9] F. Sondheimer, C. Amendolla, and G. Rosenkranz *J. Amer. Chem. Soc.* **75,** 5930 (1953).

[10] C. Djerassi, A. J. Manson, and A. Segaloff *J. Org. Chem.* **21,** 490 (1956); C. Djerassi, H. Bendas, and A. Segaloff *Ibid.* **21,** 1056 (1956).

[11] C. Djerassi, R. Riniker, and B. Riniker *J. Amer. Chem. Soc.* **78,** 6362, 6377 (1956).

[12] E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita, and M. Tishler *J. Amer. Chem. Soc.* **75,** 3477 (1953).


I
II a R=CH3CO
b R=CH3CH2CO
III a R=CH3CO
b R=CH3CH2CO
IV
V
VI a R=
OAc
H
b R=
OH
H
c R= O
VII
VIII a R=
OH
H
b R= O
IX
X
XI
XII

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3β-Acetoxy-22a,25a,5α,8α-spirostan-11-one (IIIa). The catalytic hydrogenation of the unsaturated ketone IIa was carried out in ethyl acetate or ether solution at room temperature and *c.* 2 atm pressure for 30 hr. Recrystallization from methanol yielded dimorphic crystals of the saturated ketone, m.p. 236–239° and 248–252°, $[\alpha]_D$ − 92°, $\lambda_{max}^{CHCl_3}$ 5·80 and 5·88 μ.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73·69; H, 9·38. Found: C, 73·83; H, 9·50.

The ketone did not form an oxime when heated under reflux for 16 hr in pyridine solution with hydroxylamine hydrochloride.

8-Isotigogenin acetate (IV). Into a solution of 800 mg of the 3β-acetoxy-11-ketone IIIa and 1·2 g of sodium in 50 c.c. of diethylene glycol (heated to 180°) was distilled anhydrous hydrazine until the reaction mixture boiled gently at 180°. After heating under reflux for 24 hr, sufficient hydrazine was distilled out to raise the temperature to 210° and the solution was maintained at that temperature for an additional 24 hr. After pouring into ice-water and extracting with benzene, there was isolated 680 mg of 8-isotigogenin (m.p. 211–219°), which was used directly in the next step.

Acetylation (acetic anhydride, pyridine, room temperature) of a sample and recrystallization from ethyl acetate furnished the analytical specimen of 8-isotigogenin acetate (IV), m.p. 186–189°, $[\alpha]_D$ − 10°, $\lambda_{max}^{CHCl_3}$ 5·80 and 8·0 μ.

Anal. Calcd. for $C_{29}H_{46}O_4$: C, 75·94; H, 10·11. Found: C, 75·73; H, 10·33.

Δ^{16}-3β-Acetoxy-5α,8α-pregnen-20-one (V). A mixture of 1·0 g of crude 8-*iso*tigogenin (m.p. 211–219°) and 8 c.c. of acetic anhydride was heated in a sealed tube at 190° for 10 hr, cooled, poured onto ice, and extracted with ether. The washed and dried ether solution was evaporated to dryness and the resulting oil, dissolved in 17 c.c. of 90% acetic acid and 10 c.c. of ethylene dichloride, was treated dropwise at 10° with 0·46 g of chromium trioxide in 5 c.c. of 90% acetic acid. After stirring for 2 hr at room temperature, the product was isolated by means of benzene, placed on 40 g of alkaline alumina[13] in 1:1 hexane-benzene solution, and allowed to stand for 1 hr. Elution with the same solvent mixture furnished 544 mg of colorless crystals, m.p. 166–177°, raised to m.p. 178–180° after several recrystallizations from methanol; $[\alpha]_D$ + 118°, $\lambda_{max}^{CHCl_3}$ 5·80, 6·01, and 6·28 μ, λ_{max}^{EtOH} 240 mμ, log ϵ 4·00.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77·05; H, 9·56. Found: C, 76·94; H, 9·40.

3β-Acetoxy-5α,8α-pregnan-20-one (VIa). The above Δ^{16}-20-ketone V (240 mg) in 50 c.c. of ethyl acetate was agitated with 200 mg of 5% palladized charcoal in an atmosphere of hydrogen for 2 hr. Removal of the catalyst and concentration of the solvent afforded a quantitative yield of solid which showed no significant ultra-violet absorption in the 240-mμ region. Recrystallization from aqueous methanol furnished 165 mg of crystals, m.p. 119–130°, and repeated recrystallization did not sharpen the melting-point range; $[\alpha]_D$ + 216°, $\lambda_{max}^{CS_2}$ 5·74 and 5·83 μ.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76·62; H, 10·07. Found: C, 77·01; H 10·28.

Saponification of the acetate was accomplished by heating under reflux for 2 hr with 2% methanolic potassium hydroxide solution. The free alcohol VIb crystallized from ether as needles, m.p. 184–187°, $[\alpha]_D$ + 149°, $\lambda_{max}^{CHCl_3}$ 5·88 μ.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79·19; H, 10·76. Found: C, 79·14; H, 10·76.

In order to show that the alkaline treatment had not affected the stereochemistry at C-17, a sample of the alcohol was re-acetylated and furnished the acetate VIa,

[13] G. P. Mueller, R. E. Stobaugh, and R. S. Winniford *J. Amer. Chem. Soc.* **75**, 4888 (1953).

m.p. 107–131°, $[\alpha]_D$ + 211°, the infra-red spectrum of which was identical with the acetate described above.

5α8,α-*Pregnane*-3,20-*dione* (VIc). To a stirred solution of 3β-hydroxy-5α,8α-pregnan-20-one (VIb) in 30 c.c. of acetone was added dropwise 1 c.c. of a standard chromium trioxide solution (26·7 g of chromium trioxide and 23 c.c. of conc. sulfuric acid diluted with water to 100 c.c.). After standing at room temperature for 10 min, water was added and the product was isolated in the usual manner by ether extraction; yield, 440 mg, m.p. 149–163°. Two recrystallizations from ethyl acetate led to colorless needles with m.p. 173–176°, $[\alpha]_D$ + 144°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79·70; H, 10·19. Found: C, 79.90; H, 10·31.

8-Iso*progesterone* (VII). Bromine (0·57 g) in 5 c.c. of glacial acetic acid was added dropwise to a solution of 490 mg of 5α,8α-pregnane-3,20-dione (VIc) in 10 c.c. of glacial acetic acid containing 5 drops of 4 N hydrogen bromide in acetic acid. After 5 hr at room temperature, the mixture was diluted with ice-water and the crude bromoketone was isolated with chloroform. The total product was heated under reflux for 14 hr with 2·94 g of sodium iodide in 30 c.c. of methyl ethyl ketone, the solution was diluted with water, extracted with ether, and washed well with sodium thiosulfate solution and with water. The resulting oil was dissolved in 60 c.c. of acetone and treated for 20 min in an atmosphere of carbon dioxide with chromous chloride prepared[5] from 5·0 g of chromic chloride. Extraction with ether provided 545 mg of brown oil (λ_{max}^{EtOH} 240 mμ, log ε 3·57) which was chromatographed on 20 g of ethyl acetate washed alumina. The 1:1 hexane-benzene eluates afforded 126 mg of recovered starting material (VIc), while from the benzene eluates there was obtained after crystallization 36 mg of 8-*iso*progesterone, m.p. 125–138°. Recrystallization from hexane-ether and sublimation at 160° and 0·02 mm yielded the analytical sample, m.p. 144–147°, $[\alpha]_D$ + 130°, $\lambda_{max}^{CHCl_3}$ 5·86, 5·98 and 6·12 μ, λ_{max}^{EtOH} 241 mμ, log ε 4·18.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80·21; H, 9·62. Found: C, 79·95; H, 9·67.

3β-*Hydroxy*-8α-*androstan*-17-*one* (VIIIa). When a solution of the Δ^{16}-20-ketone V in ethanol (containing 15% of pyridine) was heated under reflux for 20 min and cooled, a high melting form of its oxime crystallized; m.p. 190–202°, changed to 186–196° after recrystallization from ethanol.

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73·95; H, 9·45; N, 3·75. Found: C, 74·32; H, 9·02; N, 3·72.

Dilution of the filtrate with water and recrystallization from ethanol furnished a lower melting form of the oxime, m.p. 158–165°.

Anal. Found C, 74·21; H, 9·12; N, 3·68.

No attempt was made to establish whether these were polymorphic forms or *syn* and *anti* isomers. For the Beckmann rearrangement, 0·5 g of the oxime mixture (total product obtained in over 90% yield on diluting reacting mixture with water) in 1·5 c.c. of dry pyridine was treated at 0° with 600 mg of *p*-acetamidobenzenesulfonyl chloride. After 2 hr at 10° and 2 hr at 25°, the mixture was poured into 3 c.c. of conc. sulfuric acid and 10 g of ice and kept overnight in the ice-box. The product was filtered and saponified by heating with 2% ethanolic potassium hydroxide solution. Dilution with water and collection of the precipitate afforded 280 mg of the crude 17-ketone VIIIa, which was recrystallized three times from pentane-ether; m.p. 151–153°, $[\alpha]_D$ + 220°, $\lambda_{max}^{CHCl_3}$ 5·75 μ.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78·57; H, 10·41. Found: C, 78·59; H, 10·38.

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8α-*Androstane*-3,17-*dione* (VIIIb). The chromium trioxide oxidation of the alcohol VIIIa was carried out in the standard manner and the analytical sample was obtained from *iso*propyl ether; m.p. 168–170°, $[\alpha]_D$ + 202°, $\lambda_{max}^{CHCl_3}$ 5·75 and 5·86 μ.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79·12; H, 9·79. Found: C, 79·23; H, 9·93.

Δ^4-8α-*Androstene*-3,17-*dione* (X). The above 3,17-dione (600 mg) was treated in acetic acid solution with 2·1 equivalents of bromine and the crude 2,4-dibromo derivative (IX) (m.p. 120°, $\lambda_{max}^{CHCl_3}$ 5·76–5·80 μ) was subjected to the sodium iodide reaction and chromous chloride reduction precisely as described above for 8-*iso*progesterone. Several recrystallizations from *iso*propyl ether of the crude, crystalline dione (400 mg, m.p. 150–160°) provided 80 mg of pure unsaturated ketone, m.p. 193–197°, $[\alpha]_D$ + 329° (dioxane), $\lambda_{max}^{CHCl_3}$ 5·75, 6·00, and 6·12 μ, λ_{max}^{EtOH} 243 mμ, log ϵ 4·17.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79·68; H, 9·15. Found: C, 79·58; H, 9·20.

8-Iso*testosterone* (XII). Reduction at −5° (24 hr) of 125 mg of Δ^4-8α-androstene-3,17-dione (X) in 5 c.c. of 95% ethanol with 6 mg of sodium borohydride by the procedure of Norymberski and Woods[8] afforded 56 mg of crystals, m.p. 155–160°, and 65 mg of semicrystalline residue. Both fractions showed only a single infra-red band at 5·75 μ, indicating that the α,β-unsaturated ketone system had been reduced.

A mixture of 200 mg of Δ^4-8α-androstene-3,17-dione (X) and 120 mg of lithium aluminum hydride in 30 c.c. of tetrahydrofuran was heated under reflux for 1 hr, saturated aqueous sodium sulfate solution was added, and the inorganic salts were filtered and washed with ether. Evaporation of the dried, organic solution left an oily residue which lacked infra-red carbonyl absorption and the total product, presumably the diol XI, was shaken for 14 hr at room temperature with 4 g of manganese dioxide in chloroform solution.[9] Filtration, evaporation, chromatography on 15 g of alumina, and elution with benzene-ether (1:1) gave 81 mg of 8-*iso*testosterone with m.p. 175–185°. The analytical specimen was recrystallized from hexane-acetone, whereupon it exhibited m.p. 182–184°, $[\alpha]_D$ + 134° (dioxane), $\lambda_{max}^{CHCl_3}$ 2·95, 5·96, and 6·10 μ, λ_{max}^{EtOH} 242 mμ, log ϵ 4·18.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79·12; H, 9·79. Found: C, 78·91; H, 10·03.

We are indebted to the American Cancer Society through the Committee On Growth of the National Research Council for financial support, and to Syntex, S.A. (Mexico City) for a generous supply of steroidal starting material.

Tetrahedron, 1957, Vol. 1, pp. 28–37. Pergamon Press Ltd., London

BY-PRODUCTS OF THE PERMANGANATE OXIDATION OF STRYCHNINE

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(*Received* 28 *December* 1956)

Abstract—Hydroxydihydrostrychninone-A (I; R = OH) and hydroxycuninecarboxylic acid (III) have been identified among the oxidation products of strychnine. Several examples of the effect of a $C_{(21)}$ hydroxyl group in facilitating elimination of OR groups from $C_{(12)}$ have been noted.

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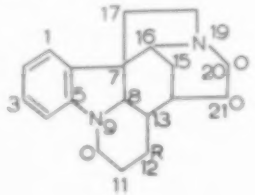
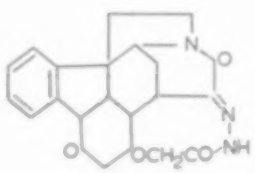
IN preparing strychninonic acid (I; R = O·CH_2·CO_2H) by the oxidation of strychnine with permanganate, Leuchs and Schwaebel[1] obtained a small quantity of a neutral compound shown later[2] to have the formula $C_{19}H_{18}O_4N_2$. We have shown, by the preparation of derivatives, the presence of a hydroxyl and a carbonyl group in this compound, suggesting that it is hydroxydihydrostrychninone-A (I; R = H). This formula was confirmed when it was found that the compound could be obtained from strychninonic acid by degradation of the acid side-chain. The sequence of reaction was essentially that employed by Leuchs and his collaborators[3] with brucinonic acid. Strychninonic acid was converted by hydrazine hydrate into the hydrazinium salt of its hydrazone. The product was contaminated by the hydrazinium salt of the azine, and could not be satisfactorily purified at this stage. Consequently it was converted into the ethyl ester and thence into strychninonic hydrazide hydrazone. The attempt to prepare this compound directly by the reaction of methyl strychninonate with hydrazine hydrate gave only a small yield of the desired product, accompanied by a compound $C_{21}H_{22}O_3N_4$, which was probably a hydrate of the cyclisation product (II) of strychninonic hydrazide. Strychninonic hydrazide hydrazone was treated with 2 moles of nitrous acid to obtain strychninonic azide. The azide when boiled in water decomposed to give a small amount of hydroxydihydrostrychninone-A (I; R = OH).



I



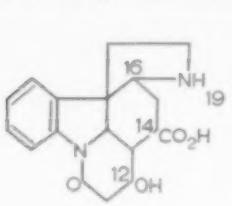
II

This compound could not be prepared by the Hofmann degradation of strychninonamide.

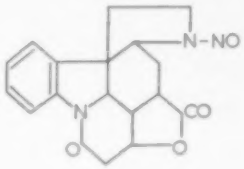
Oxidation of hydroxydihydrostrychninone-A with hydrogen peroxide in formic

[1] Leuchs and Schwaebel *Ber.* **46**, 3693 (1913).
[2] Holmes, Openshaw, and Robinson *J. Chem. Soc.* 908 (1946).
[3] Leuchs and Schneider *Ber.* **59**, 267 (1926); Leuchs and Gladkorn *Ber.* **56**, 1780 (1923); Leuchs and Kanao *Ber.* **57**, 1318 (1924).

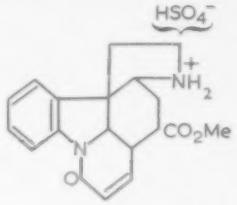
acid[4] or barium hydroxide solution[5] gave 12-hydroxycunine-14-carboxylic acid (III), isolated as a hydrochloride, $C_{18}H_{21}O_4N_2Cl,H_2O$, or a perchlorate.



III



IV



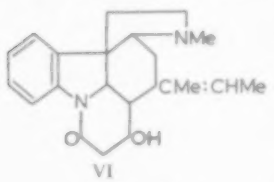
V

The hydrochloride proved to be identical with the compound obtained by Leuchs and Schwaebel[1] by treating an amorphous product from the permanganate oxidation of strychnine with methanol and concentrated hydrochloric acid. The nitroso-derivative of the acid (III) formed the lactone (IV), and the N-benzoyl derivative of the acid was partially lactonised, on crystallisation from aqueous acetic acid. The formation of these lactones indicates a *cis* configuration of the hydrogen atoms at C(12) and C(14).[6]

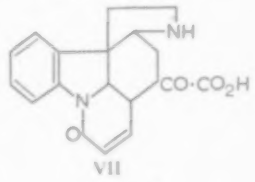
12-Hydroxycunine-14-carboxylic acid perchlorate was esterified in methanol containing a small amount of concentrated sulphuric acid to methyl dehydrocunine-carboxylate hydrogen sulphate, for which the most probable formula is (V).

Because these derivatives of cunine were obtained in small overall yield, the preparation of 12-hydroxy-14-(2-but-2-enyl)-19-methylcunine(VI) as a possible starting material for further degradations was investigated. This compound was believed to be the chief constituent of the mixture of products obtained by the Emde reduction of strychnine methosulphate.[7] The reduction of methylstrychnine by sodium in liquid ammonia[8] followed by treatment of the product with acid, afforded the compound (VI), but in very low yield.

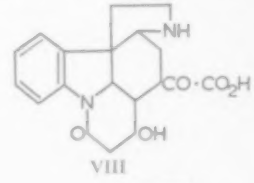
When hydroxydihydrostrychninone-A was heated with strong hydrochloric acid it was hydrolysed to an amino-acid which differed from the hydrolysis product (VII) of strychninone-A, and probably had the structure (VIII). It thus resembles



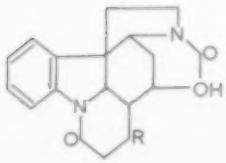
VI



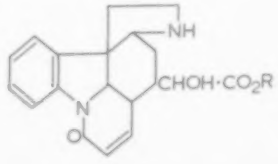
VII



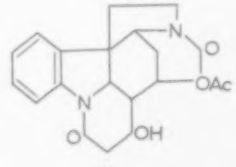
VIII



IX



X



XI

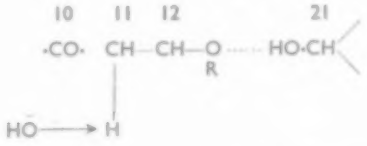
[4] Prelog and Kocor *Helv. Chim. Acta* **31**, 237 (1948).
[5] Leuchs and Kröhnke *Ber.* **65**, 980 (1932); **66**, 252 (1933).
[6] Holmes *The Alkaloids* Vol. II. p. 517. Ed. Manske and Holmes, Academic Press (1952).
[7] Perkin, Robinson, and Smith *J. Chem. Soc.* 1239 (1932); 574 (1934); Reynolds and Robinson *J. Chem. Soc.* 592 (1934).
[8] Clemo and King *J. Chem. Soc.* 1661 (1948).

strychninonic acid, which is hydrolysed to a "monohydrate" and a "dihydrate," without significant elimination of glycollic acid.[9] On the other hand, its reduction product,[2] hydroxydihydrostrychninolone-A (IX: R = OH), like strychninolic acid (IX; R = O·CH_2·CO_2H), eliminated the $C_{(12)}$ oxygen atom when heated in strong hydrochloric acid, forming the amino acid (X: R = H)[10] and when warmed in dilute alkali,[11] forming strychninolone-C.[12] In the latter instance strychninolone-A was almost certainly the primary product, but under the conditions of the experiment isomerised to strychninolone-C.

The base-catalysed elimination of water from hydroxydihydrostrychninolone-A may be reversible, for the compound, $C_{19}H_{20}O_4N_2$, isolated in low yield as a by-product of the alkaline cleavage of strychninolic acid to strychninolone-A[13] and of the base-catalysed isomerisation of strychninolone-A to strychninolone-B,[12] appears to be identical with it.

A further example of the facility with which compounds related to strychninolic acid eliminate a $C_{(12)}$ oxygen function was given by the reaction of ethyl strychninolate (IX; R = O·CH·CO_2Er) with hydrazine hydrate to afford a mixture of isomeric hydrazinodihydrostrychninolones-A, (IX; R = $NHNH_2$) instead of the expected hydrazide (IX; R = O·CH_2·$CONHNH_2$). These compounds are probably isomeric at $C_{(12)}$, being formed by addition of hydrazine to strychninolone-A; such addition to strychninolone-C proceeds much more slowly. Two isomeric aminodihydrostrychninolones have been prepared by analogous reactions between strychninolone-and ammonia.[12]

The base-catalysed fission of glycollic acid from strychninolic acid has been discussed by Woodward[14] in terms of a "push-pull" mechanism, the release of the negative glycollate ion being facilitated by hydrogen bonding from the hydroxyl



group at $C_{(21)}$ as shown. It is assumed that the cage-like structure of strychnine makes it sterically impossible for a solvent molecule to approach closely enough to form such a hydrogen bond. Hence such a mechanism is possible in strychninolic acid, but not in strychninonic acid. However, this hypothesis, though attractive in principle, does not apply so aptly to acid-catalysed eliminations.

It seems possible, from an examination of molecular models, that steric compression of the $C_{(12)}$ oxygen atom by the $C_{(21)}$ hydroxyl group may explain these results. Such interference may also explain the formation from hydroxydihydrostrychninolone-A under mild conditions of a *monoacetate*. This was shown to be the $C_{(21)}$ acetoxy compound (XI), the isomeric $C_{(12)}$ monoacetate (IX: R = OAc) being

[9] Leuchs and Reich *Ber.* **43**, 2420 (1910).
[10] Leuchs, Diels, and Dornow *Ber.* **68**, 106 (1935); Leuchs and Dornow *ibid.* p. 1786.
[11] Leuchs and Schneider *Ber.* **42**, 2494 (1909).
[12] Leuchs and Bendixsohn *Ber.* **52**, 1443 (1919).
[13] Leuchs and Schwaebel *Ber.* **47**, 1553 (1914).
[14] Woodward, quoted in ref. 6.
[15] Kotake and Mitsuwa *Bull. Chem. Soc. Japan* **11**, 231 (1936).

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obtained by hydrogenation of the acetate of hydroxydihydrostrychninone-A (I; R = OAc).

EXPERIMENTAL

(Melting points are uncorrected. Where not specified, concentrations of solutions used in the determination of specific rotation were about 0·5%.)

Strychninonic acid hydrazone. Strychninonic acid (0·48 g) was refluxed for 3 hours with hydrazine hydrate (0·28 c.c.) and absolute ethanol (6 c.c.), and the mixture then cooled in ice. The thick precipitate (0·42 g), m.p. 210–212°, was shown by analysis to be a mixture of the hydrazinium salts of the hydrazone and the azine (Found: C, 58·1; H, 5·9; N, 18·1. A mixture of 65% $C_{21}H_{26}O_5N_6$ and 35% $C_{42}H_{48}O_{10}N_{10}$ requires C, 58·1; H, 5·8; N, 18·1%).

Strychninonic hydrazide hydrazone. The mixture of the hydrazinium salts of the hydrazone and the azine (1 g) was triturated with 12% ethanolic hydrogen chloride (10 c.c.) and allowed to stand for 5 hours at room temperature. It was then poured into an ice-cold 7% solution of potassium hydrogen bicarbonate (70 c.c.), and the mixture extracted with chloroform (4 × 10 c.c.). The dried extract on evaporation gave ethyl strychninonate hydrazone as an uncrystallisable yellow oil. The ester was boiled with hydrazine hydrate (0·25 c.c.) in absolute ethanol (7 c.c.) for 20 min. The solution was concentrated, and the residue crystallised twice from ethanol to give *strychninonic hydrazide hydrazone*, sintering at 160°, decomp. 180–190° (Found: C, 58·2; H, 5·9; N, 19·4. $C_{21}H_{24}O_4N_6.\frac{1}{2}H_2O$ requires C, 58·2; H, 5·8; N, 19·4%). The filtrate, on concentration and scratching, deposited another crop of crystals, sintering at 160°, decomp. 222–230° of *hydrazide hydrazone* (Found: C, 57·9; H, 5·9; N, 19·3%) probably containing different proportions of isomerides (cf. ref. 3).

An alternative method was to reflux methyl strychninonate (0·85 g) with hydrazine hydrate (0·8 c.c.) in ethanol (15 c.c.) for 2 hours. Concentration to 10 c.c. gave impure hydrazide hydrazone (0·22 g). The filtrate on further concentration yielded a *compound* (possibly II) crystallising from ethanol as white needles, m.p. 226–228° (Found: C, 61·4; H, 5·7; N, 13·8. $C_{21}H_{22}O_5N_4$ requires C, 61·4; H, 5·4; N, 13·6%).

Strychninonic hydrazide hydrazone gave a deep red, rather then the usual blue or purple colour, in the Otto test.

Hydroxydihydrostrychninone-A (I; R = OH). Strychninonic hydrazide hydrazone (0·46 g) in 1 N hydrochloric acid (2·2 c.c.) at 0° was treated with sodium nitrite (0·15 g) dissolved in a little water. After standing for 45 min at 5–15°, the precipitate of azide was removed and heated in water (40 c.c.) at 100° for 45 min. The mixture was then made alkaline with potassium hydrogen carbonate and extracted with chloroform. The sticky residue from the chloroform dissolved in concentrated hydrochloric acid to a deep crimson solution, from which a yellow solid separated on dilution with water. It was crystallised from methanol; the first crop, a curdy yellow *solid*, decomp. 235–245°, gave a crimson colour in hydrochloric acid (Found: C, 59·2; H, 5·6; N, 16·6. $C_{21}H_{24}O_5N_5$ requires C, 59·1; H, 5·7; N, 16·4%). The filtrate was treated with charcoal and concentrated; on cooling, tiny, white needles of hydroxydihydrostrychninone-A separated, sintering at 317°, m.p. 327–328°, undepressed by admixture with material from the oxidation of strychnine.

The yield from this reaction was unfavourable, and all further experiments on hydroxyhydrostrychninone-A were carried out with material from the oxidation of

strychnine.[1,2] The compound (and many related compounds) showed widely varying melting-points, depending on the solvent from which it had been crystallised. Thus it crystallised from water in needles, m.p. 330–334°, $[\alpha]_D^{20}$, −16° (*c.* 0·37 in acetic acid), −74° (*c.* 1·01 in pyridine, λ_{max}^{EtOH}, 2500 Å; log ε_{max}, 4·1, while it separated from concentrated hydrochloric acid on dilution with water in microscopic prisms, m.p. 350–354°, $[\alpha]_D^{20}$, −17° (*c.* 0·36 in acetic acid), −73° (*c.* 0·74 in pyridine) (Found: C, 67·3; H, 5·5; N, 8·3. Calc. for $C_{19}H_{18}O_4N_2$: C, 67·4; H, 5·4; N, 8·3%). It crystallised from methanol in small needles, m.p. 328–330°, and from ethanol in needles, m.p. 330–332°, showing the same optical rotation and giving the same results on analysis as the forms above.

The *p*-nitrophenylhydrazone crystallised from aqueous acetic acid as microscopic, yellow rods, m.p. 299–300° (Found: C, 62·8; H, 4·9; N, 14·4. $C_{25}H_{23}O_5N_5$ requires C, 63·3; H, 5·0; N, 14·8%). It gave a deep magenta coloration in alcoholic sodium hydroxide.

The *semicarbazone* crystallised from aqueous methanol in minute needles, sintering at 210°, decomp. 230–232°, $[\alpha]_D^{21}$, 340° (*c.* 0·44 in acetic acid), $[\alpha]_D^{17}$, 344° (*c.* 0·554 in acetic acid) (Found: C, 60·6; H, 5·4; N, 17·2. $C_{20}H_{21}O_4N_5$ requires C, 60·7; H, 5·4; N, 17·7%).

The oxime, after two crystallisations from methanol, was obtained as needles, m.p. 297–302° (frothy decomp.), $[\alpha]_D^{20}$, −6° (*c.* 0·31 in acetic acid) (Found: C, 64·6; H, 5·4; N, 11·4. $C_{19}H_{19}O_4N_3$ requires C, 64·7; H, 5·4; N, 11·9%).

The *acetate* (I; R = OAc), prepared by heating a suspension of hydroxydihydrostrychninone-A in acetic anhydride containing one drop of 60% perchloric acid for 1 hour at 100°. It separated on cooling the mixture as microscopic rhombs, blackening at 250°, m.p. 265–266°, $[\alpha]_D^{16}$, 38°, 36° (acetic acid) (Found: C, 65·6,66·1, 65·8; H, 5·2, 6·0, 5·3; N, 7·7. $C_{21}H_{20}O_5N_2$ requires C, 66·3; H, 5·3; N, 7·4%). The acetate prepared with pyridine-acetyl chloride darkened at 236°, m.p. 241–242°. Acetylation by boiling acetic anhydride gave large crystals sintering at 235°, m.p. 238–241°. Any of these different forms crystallised from ethanol in needles, m.p. 230–237°. All forms gave the same analytical results and had the same optical rotation.

The *benzoate* (I; R = OBz) crystallised from alcohol in minute needles, m.p. 224–226°, $[\alpha]_D^{18}$, +140° (*c.* 0·45 in acetic acid) (Found: C, 70·5, 70·8; H, 5·1, 5·4. $C_{26}H_{22}O_5N_2$ requires C, 70·6; H, 5·0%) and was precipitated from pyridine solution by ethanol as an amorphous solid, m.p. 235–238°, $[\alpha]_D^{15}$, 143° (*c.* 0·66 in acetic acid) (Found: C, 70·8; H, 5·1%).

Strychninonamide (I; R = O·CH_2·$CONH_2$). Strychninonic acid (0·8 g) in chloroform (10 c.c.) was refluxed with thionyl chloride (1 c.c.) for 1 hour. The residue after evaporation under reduced pressure was shaken with concentrated ammonium hydroxide (5 c.c.), and gave *strychninonamide* (0·5 g), sintering and darkening at 280°, m.p. 295–296°, $[\alpha]_D^{19}$, +53° (*c.* 0·67 in acetic acid) (Found: C, 63·8; H, 5·3; N, 10·2. $C_{21}H_{21}O_5N_3$ requires C, 63·8; H, 5·4; N, 10·6%). The amide crystallised from water as white, microscopic rhombs, m.p. 260–262°, $[\alpha]_D^{19}$, +58° (*c.* 0·29 in acetic acid) (Found: C, 63·2; H, 5·3; N, 11·0%).

In an attempted repetition of this preparation, using strychninonic acid (5 g) and thionyl chloride (7 c.c.) in chloroform (50 c.c.), a *neutral* isomer of strychninonic acid was obtained, sintering at 210°, m.p. 253–258°. After two recrystallisations from

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methanol it was obtained as long needles, sintering at 220°, m.p. 238–245°, $[\alpha]_D^{19}$, —81° (*c.* 0·37 in acetic acid), λ_{max}^{EtOH} 2500 Å, log ε_{max} 4·1 (Found in air-dried material: C, 61·5, 61·3, 60·8; H, 5·8, 4·9, 5·7; N, 6·9, 6·9, 6·9; loss at 130°/1 mm: 3·5. $C_{21}H_{20}O_6N_2,\frac{3}{4}H_2O$ requires C, 61·5; H, 5·3; N, 6·7; H_2O, 3·3%. Found in material dried at 130°/10 mm: C, 64·1; H, 5·3; N, 7·1; M, cryoscopic in camphor, 536. $C_{21}H_{20}O_6N_2$ requires C, 63·7; H, 5·0; N, 7·1%; M, 396). The solid gave a positive Otto reaction, and was insoluble in dilute mineral acid and sodium carbonate solution.

Its p-*nitrophenylhydrazone* crystallised from aqueous acetic acid as microscopic, yellow prisms, m.p. 240–242° (Found: C, 59·8; H, 5·5; N, 12·6. $C_{27}H_{25}O_7N_5{\cdot}H_2O$ requires C, 59·0; H, 4·9; N, 12·7%). It was insoluble in dilute sodium hydroxide and on addition of ethanol to the mixture a deep magenta colour appeared. The formation of this derivative excludes the hydroxylactone possibility, and the substance would appear to be the hydrate of an anhydro-strychninonic acid.

The isomeric p-*nitrophenylhydrazone of strychninonic acid* crystallised from acetic acid in microscopic yellow rods, sintering at 216°, m.p. 219–221° (Found in material dried at 120° in vacuum: C, 58·7; H, 5·1. $C_{27}H_{25}O_7N_5H_2O$ requires C, 59·0; H, 4·9%). It gave a light-red colour with ammonium hydroxide, and a deep magenta solution with dilute sodium hydroxide.

12-*Hydroxycunine*-14-*carboxylic acid* (III). (a) *From the permanganate oxidation of strychnine*. The compound, prepared according to Leuchs and Schwaebel,[1] crystallised from a small quantity of water (charcoal) as glistening, white rods, m.p. 297–298°, $[\alpha]_D^{18}$, —46° (*c.* 0·52 in 8% aqueous ammonia) (Found: loss at 100°/0·1 mm, 4·6. Calc. for $C_{18}H_{21}O_4N_2Cl{\cdot}H_2O$: H_2O, 4·7. Found: C, 59·2, 59·8; H, 5·8, 5·2; Cl, 9·7. $C_{18}H_{21}O_4N_2Cl$ requires C, 59·3; H, 5·8; Cl, 9·8%).

The compound gave a faint, evanescent coloration in the Otto test.

(b) *From the oxidation of hydroxydihydrostrychninone-A with hydrogen peroxide and barium hydroxide*. Hydroxydihydrostrychninone-A (2·5 g) suspended in 5% barium hydroxide (60 c.c.) and perhydrol (1·7 c.c.) was heated on the steam-bath for 15 min with occasional shaking. The cooled mixture was made faintly acid with dilute sulphuric acid and filtered. Next day a small amount of brownish precipitate was removed, and 60% perchloric acid (4·4 c.c.) added gradually to the filtrate. After some brown gums had separated, hydroxycuninecarboxylic acid perchlorate was obtained; after two crystallisations from water it blackened at 255°, m.p. 262–263°, $[\alpha]_D^{18}$, —42° (*c.* 0·53 in 8% aqueous ammonia) (Found: C, 50·7; H, 5·0. $C_{18}H_{21}O_8N_2Cl$ requires C, 50·4; H, 4·9%). The perchlorate was identical with that obtained by treating a hot solution of Leuchs and Schwaebel's hydrochloride with sodium perchlorate.

Methyl-11-*dehydrocunine*-14-*carboxylate* (V). Hydroxycuninecarboxylic acid perchlorate (0·25 g) was refluxed for 1½ hours in methanol (5 c.c.) containing concentrated sulphuric acid (0·08 c.c.). The mixture on cooling to —10° deposited microscopic rhombs (0·19 g) of the *methyl ester hydrogen sulphate*, softening at 190°, decomp. 237°, $[\alpha]_D^{23}$, +30° (*c.* 1·28 in water) (Found: C, 54·2; H, 5·1; S, 7·1; MeO, 6·6. $C_{19}H_{20}O_3N_2,H_2SO_4$ requires C, 54·0; H, 5·3; S, 7·6; MeO, 7·3%). It gave no perceptible colour in the Otto test.

18-*Nitroso*-12-*hydroxycunine*-14-*carboxylic acid*. N-Hydrochloric acid (4 c.c.) was added with shaking to a solution of hydroxycuninecarboxylic acid hydrochloride

(0·32 g) and sodium nitrite (0·06 g) dissolved in 0·25 N sodium hydroxide (13 c.c.). After 5 min the faintly yellowish *nitroso acid* was removed. It softened above 50°, and melted between 150° and 180° (Found: C, 60·3; H, 5·4; N, 11·8. $C_{18}H_{19}O_5N_3$ requires C, 60·5; H, 5·4; N, 11·8%). It was soluble in cold sodium carbonate solution. When crystallised from aqueous acetic acid, it changed to the nitroso-lactone (IV) sintering at 247°, m.p. 255–257° (Found: C, 63·2; H, 5·3. $C_{18}H_{17}O_4N_3$ requires C, 63·7; H, 5·0%). The lactone was insoluble in cold dilute alkali, but dissolved on warming. It gave a deep purple colour in the Otto reaction.

18-*Benzoyl*-12-*hydroxycunine*-14-*carboxylic acid*. Hydroxycuninecarboxylic acid perchlorate (0·38 g) in N-sodium hydroxide (2·5 c.c.) was treated with benzoyl chloride (0·09 c.c.). After shaking for 30 min, the solution was decanted from a small amount of gum and acidified. The flocculent white precipitate crystallised from aqueous acetic acid as a mixture of *lactone* and *acid*, m.p. 170–180°, with previous sintering (Found: C, 70·8; H, 5·1; N, 6·5; acid equivalent, 597, 600. A mixture of 72% $C_{25}H_{24}O_5N_2$ –28% $C_{25}H_{22}O_4N_2$ requires C, 70·3; H, 5·5; N, 6·6%; acid equivalent 600). The solid was partially soluble in cold sodium carbonate solution, but dissolved completely on warming. It gave a deep blue colour in the Otto test.

12-*Hydroxy*-14-(2′-*but*-2-*enyl*)-19-*methylcunine* (VI). Sodium (2·1 g) was added during 20 min to a stirred suspension of finely-ground methylstrychnine (3·7 g) in liquid ammonia (200 c.c.). Methanol (10 c.c.) was added, and the ammonia allowed to evaporate. The aqueous solution of the residue gave on acidification a gum, which dissolved almost completely in hot 20% hydrochloric acid. The base separating when this solution was made alkaline was taken up in benzene and chromatographed on alumina, giving 12-hydroxy-14-(2′-but-2′-enyl)-19-methylcunine as a first fraction: after six crystallisations from light petroleum (b.p. 40–60°), rods, m.p. 122–125° (0·1 g) were obtained (Found: C, 75·4; H, 8·1; C-Me, 11·1; NMe, 5·7. $C_{22}H_{28}O_2N_2$ requires C, 75·0; H, 7·9; 2C-Me, 15·3; NMe, 8·2%).

The perchlorate, crystallised twice from water, was obtained in tiny spherulites, darkening at 250°, m.p. 264–166° (decomp.) (Found: C, 58·4; H, 6·7; N, 6·9; Cl, 7·2. $C_{22}H_{29}O_6N_2Cl$ requires C, 58·3; H, 6·5; N, 6·2; Cl, 7·8%).

12-*Hydroxy*-14-*hydroxyoxalylcunine* (VIII). Hydroxydihydrostrychninone-A (0·7 g), when heated with concentrated hydrochloric acid (3 c.c.) on the steam-bath for 30 min; afforded, on cooling, the *amino-acid hydrochloride*, softening and darkening above 250°, decomp, about 310°, unaltered by recrystallisation from water, $[\alpha]_D^{18}$, +14° (*c*. 0·50 in water), λ_{max}^{EtOH} 2500 Å, log ε_{max} 4·1 (Found in air-dried material: C, 55·8; H, 5·8; Cl, 8·9. $C_{19}H_{21}O_5N_2Cl,H_2O$ requires C, 55·5; H, 5·6; Cl, 8·6%. Found in material dried at 130°/10 mm: C, 57·6; H, 5·8; Cl, 9·8. $C_{19}H_{21}O_5N_2Cl$ requires C, 58·1; H, 5·4; Cl, 9·0%). It gave no coloration in the Otto test. When crystallised twice from methanol, the amino-acid hydrochloride formed the *methyl ester*, decomp, 270° (Found in material dried at 130°/10 mm: C, 59·1; H, 5·8; Cl, 7·9; MeO, 6·6. $C_{20}H_{23}O_5N_2Cl$ requires C, 59·0; H, 5·7; Cl 8·7; MeO, 7·6%). The ester gave a brownish Otto reaction.

Strychninone-A. The directions of Holmes, Openshaw, and Robinson[2] were followed, except that it was found necessary to warm the reaction mixture for 1 hour on the steam-bath. The crude strychninone-A in benzene was chromatographed on alumina, from which it was eluted by chloroform, giving a white solid sintering at 220°, m.p. 237–247°, $[\alpha]_D^{25}$, —143° (*c*. 3·73 in acetic acid) (Found: C, 71·0; H, 5·0. Calc.

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for $C_{19}H_{18}O_2N_2$: C, 71·2; H, 5·0%). When strychninone-A was crystallised from ethanol, it first separated in micaceous plates, sintering at 220°, m.p. 240–246° (Found: C, 68·3; H, 6·1; N, 7·8, loss at 130°/mm, 10·5. Calc. for $C_{19}H_{18}O_2N_2$, C_2H_6O: C, 68·8; H, 6·1; N, 7·7; loss, 12·6%) and as a later crop of tufts of tiny needles, sintering at 228°, m.p. 246–249° (Found: C, 68·0; H, 6·1; N, 8·0%) (cf. ref. 2). The *semicarbazone* crystallised from the aqueous reaction mixture as pale yellow, microscopic rods, foamy decomp. 208–209°, $[\alpha]_D^{16}$, +148° (*c*. 1·07 in acetic acid) (Found: C, 60·1; H, 5·1; N, 17·6. $C_{20}H_{19}O_2N_5.H_2O$ requires C, 60·7; H, 5·4; N, 17·7%). The *oxime* softened at 215°, m.p. 224–228° (Found: C, 64·7; H, 5·5; N, 11·5. $C_{19}H_{17}O_2N_3.H_2O$ requires C, 64·7; H, 5·4; N, 11·9%). The p-*nitrophenylhydrazone* crystallised from aqueous acetic acid as microscopic, yellow rods, sintering at 242°, m.p. 250–253° (Found in material dried at 120°/0·1 mm: C, 66·0; H, 5·1; N, 15·4. $C_{25}H_{21}O_4N_5$ requires C, 65·9; H, 5·2; N, 15·4%).

11-*Dehydro*-14-*hydroxyoxalylcunine* (VII). Strychninone-A (0·1 g) in concentrated hydrochloric acid (1 c.c.) was heated to 100° for 1 hour. The dirty brown solid separating from the mixture on cooling was dissolved in water (2 c.c.) and filtered. Dilution with acetone precipitated a tar; the residual solution on evaporation yielded 11-*dehydro*-14-*hydroxyoxalylcunine* softening at 290°, decomp. 232–337° (Found: C, 58·2; H, 5·3; Cl, 9·7. $C_{19}H_{19}O_4N_2Cl.H_2O$ requires C, 58·1; H, 5·4; Cl, 9·0%). λ_{max}^{EtOH} 2500 Å, log ε_{max} 4·1. It gave a feeble Otto reaction.

Chlorodihydrostrychninone-A (I; R = Cl). A suspension of hydroxydihydrostrychninone-A (2 g) in dry chloroform (30 c.c.) and thionyl chloride (2 c.c.) was shaken occasionally for two days. The solution was then washed with water and dilute ammonia, dried, boiled with Fuller's earth, and concentrated. Several crops of sticky solids were obtained which on recrystallisation from chloroform gave a white solid (0·17 g), m.p. 225–226° (Found: C, 63·9; H, 5·1; Cl, 9·9. $C_{19}H_{17}O_2N_2Cl$ requires C, 63·9; H, 4·8; Cl, 9·9% as well as larger amounts (0·77 g) melting between 220° and 224°). Attempts to dehydrohalogenate this compound with pyridine to form strychninone-A were fruitless.

Hydroxydihydrostrychninolone-A (IX: R = OH). Hydroxydihydrostrychninone-A (6·75 g) in acetic acid (100 c.c.) was hydrogenated in the presence of platinum oxide (0·65 g) to give hydroxydihydrostrychninolone-A[2] (0·65 g), m.p. 300–301°, $[\alpha]_D^{20}$, +26° (acetic acid) (Found: C, 66·9; H, 6·0. Calc. for $C_{19}H_{20}O_4N_2$: C, 67·0; H, 5·9%). It crystallised from methanol in needles, m.p. 260–270°, $[\alpha]_D^{20}$, +26° (acetic acid) (Found: C, 66·4, 66·5; H, 5·7, 6·0%; no loss at 100°/0·1 mm), and from water in tiny, felted needles, m.p. 270–280° (Found: C, 67·2; H, 6·0%).

Oxidation of hydroxydihydrostrychninolone-A to hydroxydihydrostrychninone-A. Chromic anhydride (0·13 g) in water (0·5 c.c.) and acetic acid (12 c.c.) was added with shaking to a suspension of hydroxydihydrostrychninolone-A (0·68 g) in acetic acid (100 c.c.). After two days the solution was concentrated under reduced pressure, diluted with water, and extracted with chloroform (6 × 15 c.c.). The chloroform solution was washed with dilute ammonia and concentrated to 10 c.c. to give a first crop of a mixture of compounds. Further concentration gave a crop of hydroxydihydrostrychninone-A, m.p. 319–325°; after two precipitations from concentrated hydrochloric acid solution by water the m.p. was 348–350°, undepressed by admixture with authentic material (Found: C, 67·1; H, 5·4. Calc. for $C_{19}H_{18}O_4N_2$: C, 67·4; H, 5·4%).

Strychninolone-C. (*a*) *From hydroxydihydrostrychninolone-A.* Hydroxydihydrostrychninolone-A (0·97 g) in N-sodium hydroxide (3·6 c.c.) was heated on the steam-bath for 90 min. The solid (0·72 g) which separated was taken up in benzene and chromatographed on alumina. Elution with carbon tetrachloride-alcohol gave strychninolone-C,[12] sintering at 237°, m.p. 246–249° without foaming, $[\alpha]_D^{23}$, −177° (*c.* 0·73 in acetic acid) (Found: C, 70·5; H, 5·8; N, 8·9. Calc. for $C_{19}H_{18}O_3N_2$: C, 70·8; H, 5·6; N, 8·7%). (*b*) *From strychninolone-A.* The following method was more convenient than those already reported.[12,15] Crude strychninolone-A (0·65 g) in 4% sodium hydroxide solution (5 c.c.) was digested for 6 hours on the steam-bath.

The crude strychninolone-C was purified by passing it in chloroform (20 c.c.) through a short column of activated alumina, which was then washed with more chloroform (20 c.c.). The combined percolates gave strychninolone-C (0·48 g), m.p. 254–250°.

11-*Dehydro*-14-*methoxycarbonylhydroxymethylcunine* (X; R = Me)—(*a*) *From hydroxydihydrostrychninolone-A.* Hydroxydihydrostrychninolone-A (0·5 g) in concentrated hydrochloric acid (5 c.c.) was heated on the steam-bath for 40 min. The solution was evaporated to dryness, the residue taken up in water and neutralised to pH7, and again evaporated to dryness. The residue was extracted with hot methanol. The solid separating from the solution was recrystallised twice from methanol, giving needles of the methyl ester hydrochloride,[10] sintering at 297°, m.p. 301–303°, $[\alpha]_D^{27}$, +9° (*c.* 0·16 in water) (Found: C, 61·0; H, 6·0; Cl, 9·3; MeO, 7·4. Calc. for $C_{20}H_{22}O_4N_2Cl$: C, 61·5; H, 5·9; Cl, 9·1; MeO, 7·9%).

The *nitrosamine* formed from the methyl ester had m.p. 215–217° (Found: C, 62·0; H, 5·6; N, 10·6. $C_{20}H_{21}O_5N_3$ requires C, 62·7; H, 5·5; N, 11·0%).

(b) *From strychninolic acid.* The acid (1 g) was heated in concentrated hydrochloric acid (7 c.c.) on the steam-bath for 1 hour. The syrup obtained on evaporation of the solution was refluxed with methanol (10 c.c.) and hydrochloric acid (0·2 c.c.) for several hours to give the ester hydrochloride (0·1 g). After one crystallisation from water the tiny needles had m.p. 301–303°, $[\alpha]_D^{20}$, +8° (*c.* 0·36 in water) (Found: C, 61·9; H, 5·8%).

Ethyl strychninolate (IX; R = OCH_2CO_2Et). Strychninolic acid (1 g) was shaken in 5% ethanolic hydrogen chloride (20 c.c.) at 0° and the mixture allowed to attain the room temperature. After 25 min the solution was neutralised with ice-cold 5% potassium hydrogen carbonate solution, and extracted with chloroform (4 × 10 c.c.). The residue from the chloroform crystallised from ethanol as microscopic prisms of *ethyl strychninolate* softening at 157°, m.p. 161–163°, $[\alpha]_D^{17}$, +27° (*c.* 0·77 in acetic acid) (Found: C, 64·0; H, 6·5; EtO, 10·1. $C_{23}H_{26}O_6N_2$ requires C, 64·8; H, 6·2; EtO, 10·5%).

Hydrazinodihydrostrychninolone-A (IX; R=$NHNH_2$)—(*a*) *From ethyl strychninolate.* Ethyl strychninolate (4·0 g) and hydrazine hydrate (1·6 c.c.) in ethanol (20 c.c.) were heated for 5 min on the water-bath and the solution than evaporated to dryness. On adding ethanol (16 c.c.) to the yellow syrup, a white crystalline solid was obtained; concentration of the filtrate gave further amounts. The gummy solid (3·0 g) was digested twice with ethanol (30 c.c.) leaving microscopic rods, sintering at 220°, m.p. 228–230°, $[\alpha]_D^{20}$, −88° (*c.* 0·69 in acetic acid) (Found: C, 64·2, 64·9; H, 6·2, 6·4; N, 16·3, 15·1. $C_{19}H_{22}O_3N_4$ requires C, 64·4; H, 6·3; N, 15·8%).

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Hydrazino dihydrostrychninolone-A was soluble in dilute hydrochloric acid and sparingly soluble in hot water. It gave a deep red colour in the Otto test.

Final concentration of the original filtrate and of the filtrates from the digestion left a white solid which, after digestion with ethanol (10 c.c.), gave an impure *isomeric hydrazinodihydrostrychninolone*-A sintering at 280°, decomp. 283–286° (Found: C, 63·2, 63·5; H, 6·1, 6·2; N, 14·9, 16·2%). These hydrazinodihydrostrychninolones on repeated crystallisation from ethanol deteriorated to brown gums.

(*b*) *From strychninolone-A*. Strychninolone-A (0·8 g) was heated on the water-bath with hydrazine hydrate (0·3 c.c.) in absolute ethanol (4 c.c.). It rapidly dissolved, then microscopic white prisms (0·49 g) separated, decomp. 222–230°, $[\alpha]_D^{20}$, −100° (*c*. 0·79 in acetic acid) (Found: C, 64·1; H, 7·0; N, 15·8%). The difference in specific rotation of the material prepared from ethyl strychninolate is probably due to difference in the proportions of isomerides.

Action of hydrazine on strychninolone-C. Strychninolone-C (0·7 g), heated in ethanol (4 c.c.) containing hydrazine hydrate (0·3 c.c.) for six hours on the steam-bath, went very slowly into solution. Next day, round, white nodules of a mixture (0·55 g) of *hydrazinodihydrostrychninolone-C* and strychninolone-C, sintering at 170°, decomp. 185–200°, were collected (Found: C, 65·8; H, 6·3; N, 14·7. A mixture of 80% $C_{19}H_{22}O_3N_4$ and 20% $C_{19}H_{18}O_3N_2$ requires C, 65·6; H, 6·3; N, 14·5%). The material was partially soluble in dilute hydrochloric acid, and gave a red Otto reaction.

$C_{(21)}$*Monoacetate of hydroxydihydrostrychninolone-A* (XI). Obtained by treatment of hydroxydihydrostrychninolone-A with acetic anhydride-sodium acetate at 100°, the *acetate* crystallised from methanol in microscopic prisms, m.p. 234–236°, $[\alpha]_D^{22}$, −24° (*c*. 1·07 in acetic acid) (Found: C, 65·6, 65·6; H, 5·8, 5·8; Ac, 13·6. $C_{21}H_{22}O_5N_2$ requires C, 65·9; H, 5·7; Ac, 11·2%).

$C_{(12)}$–*Monoacetate of hydroxydihydrostrychninolone-A* (IX; R = OAc). Hydroxydihydrostrychninone-A acetate (1·0 g) in acetic acid (80 c.c.) with platinum oxide (0·02 g) was hydrogenated to give the $C_{(12)}$–*monoacetate* (0·9 g), m.p. 235–239°, obtained after two recrystallisations from methanol as needles, sintering at 205°, m.p. 215–217°, $[\alpha]_D^{20}$, +91° (*c*. 0·91 in acetic acid) (Found: C, 65·7; H, 5·7. $C_{21}H_{22}O_5N_2$ requires C, 65·9; H, 5·7%).

Analyses were carried out by Dr. F. B. Strauss and Dr. G. Weiler, also by Mr. F. Hall. Grateful acknowledgement is made to the Royal Commission for the Exhibition of 1851 for a Science Scholarship (to J. T. E.).

Tetrahedron, 1957, Vol. 1, pp. 38–44. Pergamon Press Ltd., London

SYNTHESES IN THE QUINAZOLONE SERIES—VI
THE SYNTHESIS OF 1:2:3:4-TETRAHYDRO-2-ARYL-4-OXOQUINAZOLINES

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(*Received 5 February* 1957)

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Abstract—An investigation of the isomeric change of N^2-arylideneorthanilamides has led to the synthesis of a new series of 1:2:3:4-tetrahydro-4-oxoquinazolines from which the corresponding quinazol-4-ones have been obtained by oxidation. Based on the present investigation, a new synthesis of 2-(*o*-aminophenyl)-3*H*-quinazol-4-one (VI) is also reported.

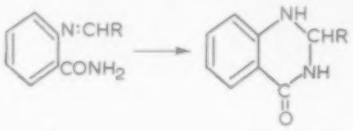
N^2-ARYLIDENEORTHANILAMIDES (I), which are readily prepared by condensing aromatic aldehydes with anthranilamide (Table 1), are characterised by the ease with which they isomerise to give 1:2:3:4-tetrahydro-2-aryl-4-oxoquinazolines (II) (Table 3). Isomerisation (Table 2) is readily effected in most cases by treating arylideneorthanilamides with dilute (8%) sodium hydroxide. In some instances dilute hydrochloric acid brought about the change, but this was invariably accompanied by partial hydrolysis of the orthanilamide. Heating under reduced pressure above the melting-point was sufficient in some instances to bring about isomerisation, which could be readily observed, since the oxoquinazolines have a higher melting-point than the corresponding arylideneorthanilamides. It is of interest to note that during the isomerisation of N^2-(*m*-nitrobenzylidene)- and N^2-(*p*-nitrobenzylidene)-orthanilamides under reduced pressure at the melting-point, oxidation takes place with the formation of 2-*m*-nitrophenyl-3*H*- and 2-*p*-nitrophenyl-3*H*-quinazol-4-one respectively. N^2-(*o*-nitrobenzylidene)-orthanilamide isomerises at the melting-point without oxidation and yields 1:2:3:4-tetrahydro-2-(*o*-nitrophenyl)-4-oxoquinazoline. A number of tetrahydro-4-oxoquinazolines have been oxidised with potassium permanganate in acetone to give the corresponding quinazol-4-ones, and the latter were identified by comparing with the same compounds already prepared by Stephen and Wadge.[1] The ease with which the hydrogen atoms in positions 1 and 2 in the tetrahydro-4-oxoquinazolines are removed by oxidation is indicated in the case of 1:2:3:4-tetrahydro-2-styryl-4-oxoquinazoline, the styryl radical remaining intact during oxidation.

The intermediate arylideneorthanilamides from the condensations of benzaldehyde *p*-methylbenzaldehyde, and piperonal with anthranilamide could not be isolated, since they isomerised rapidly to the corresponding 4-oxoquinazolines during their preparation.

In a previous communication[2] it has been shown that the condensation of 4-chloroquinazoline with methyl anthranilate gives methyl *N*-4-quinazolinyl-anthranilate (III), which with hydrogen chloride cyclises with elimination of methanol to quinazo-[4,3-*b*]quinazol-8-one (IV), and the latter has also been obtained by hydrolysis of 3-4′-quinazolinylquinazol-4-one (V).[3] Further hydrolysis of (IV) gives 2-(*o*-aminophenyl)-3*H*-quinazol-4-one (VI), the structure of which has now been confirmed by the

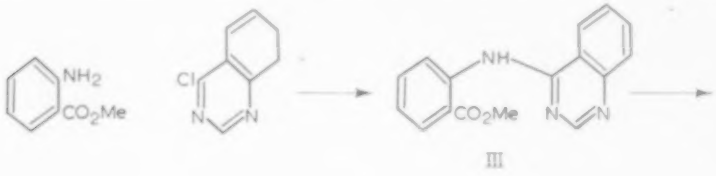
[1] H. Stephen and G. Wadge *J. Chem. Soc.* 4420 (1956).

preparation of N^2-(*o*-nitrobenzylidene)orthanilamide (VII), which as stated above is isomerised to give 1:2:3:4-tetrahydro-2-(*o*-nitrophenyl)-4-oxoquinazoline (VIII), and the latter on oxidation gives 2-(*o*-nitrophenyl)-3*H*-quinazol-4-one, which on reduction is converted into 2-(*o*-aminophenyl)-3*H*-quinazol-4-one identical with (VI), and on treatment with anhydrous formic acid yields (IV).



I II

In the preliminary stages of the present investigation it was intended to prepare methyl arylideneanthranilates with the object of their conversion to 1:2:3:4-tetrahydro-4-oxoquinazolines by the action of ammonia. Attempts to condense benzaldehyde with methyl anthranilate in ethanol in presence of hydrogen chloride gave a mixture of



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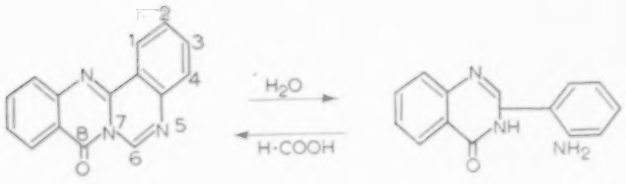
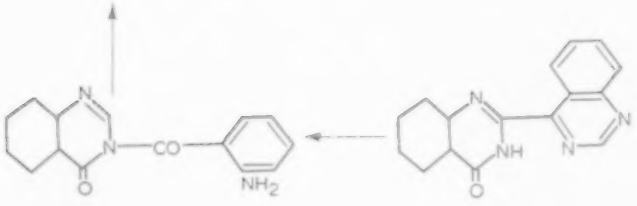
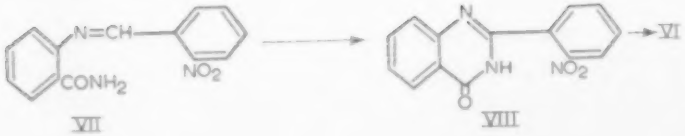


IV VI



V

Intermediate compound not isolated



VII VIII

[di-(*o*-methoxycarbonylanilino)methyl] benzene (IX) and 1:2:3:4-tetrahydro-3-*o*-methoxy-carbonylphenyl-4-oxo-2-phenylquinazoline (X). In absence of hydrogen chloride, methyl anthranilate in ethanol combined with benzaldehyde and *p*-methylbenzaldehyde to give respectively methyl *N*-(α-hydroxybenzyl)orthanilate (XI) and methyl *N*-(α-hydroxy-4-methylbenzyl)orthanilate (XII), which on treatment with ammonia gave 1:2:3:4-tetrahydro-2-phenyl-4-oxoquinazoline (XIII), and 1:2:3:4-tetrahydro-2-*p*-tolyl-4-oxoquinazoline (XIV) respectively. These reactions are very slow, requiring from two to three weeks.

IX X

XI XII

XIII XIV

EXPERIMENTAL

Preparation of N[2]*-arylideneorthanilamides.* Anthranilamide (1 mol) and aromatic aldehyde (1 mol) were mixed and dissolved in ethanol, and after refluxing the solution for a few minutes the condensation product crystallised on cooling (Table 1), and was purified by recrystallisation from ethanol.

Isomerisation of arylideneorthanilamides to 1:2:3:4-*tetrahydro*-2-*aryl*-4-*oxoquinazolines.* (a) Refluxing the orthanilamide with *N* hydrochloric acid for ½ hour was sufficient in most cases to effect partial isomerisation, which was usually accompanied by hydrolysis of some of the amide. (b) Refluxing with 2 N sodium hydroxide solution with addition of ethanol to increase solubility of the amide brought about isomeric change usually in good yield. In those instances in which hydroxyl is present in the aryl radical, the oxoquinazoline is precipitated by addition of acetic acid. (c) Heating above the melting-point under reduced pressure resulted in rapid isomerisation in a few cases in good yield.

[1] T. Stephen and H. Stephen *J. Chem. Soc.* 4174 (1956).
[2] T. Stephen and H. Stephen *J. Chem. Soc.* 4178 (1956).

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TABLE 1.—N^2-ARYLIDENEORTHANILAMIDES

Ar	Found (%)						Required (%)	
	Yield (%)	m.p.	Form	C	H	Formula	C	H
o-C_6H_4(OH)	81	165	orange needles	70·28	5·18	$C_{14}H_{12}O_2N_2$	70·0	5·04
o-C_6H_4(OMe)	77	159	pale yellow needles	70·66	5·7	$C_{15}H_{14}O_2N_2$	70·87	5·51
m-C_6H_4(OH)	70	146	yellow needles	70·28	5·39	$C_{14}H_{12}O_2N_2$	70·0	5·04
p-C_6H_4(OH)	70	160	yellow needles	70·4	5·22	do	do	do
p-C_6H_4(OMe)	61	158	pale yellow needles	70·78	5·64	$C_{15}H_{14}O_2N_2$	70·87	5·51
2:4-$C_6H_3(OH)_2$	90	190	orange needles	N,9·16,9·45			N,9·27	
2:4-$C_6H_3(OMe)_2$	88	160	yellow needles	67·42	5·69	$C_{16}H_{16}O_3N_2$	67·61	5·73
2:4-$C_6H_3(OEt)_2$	87	177	yellow needles	69·2	6·62	$C_{18}H_{20}O_3N_2$	69·23	6·46
2:4-C_6H_3(OEt)(OH)	72	180	yellow needles	67·43	6·86	$C_{16}H_{16}O_3N_2$	67·61	5·73
2:4-C_6H_3(OH)(OEt)	66		see Note (a)					
3:4-C_6H_3(OH)(OMe)	50	153	yellow needles	see Note (b)				
3:4-C_6H_3(OMe)(OH)	81	187	yellow needles	see Note (c)				
3:4-C_6H_3(OEt)(OH)	97	187	pale yellow needles	67·44	5·52	$C_{16}H_{16}O_3N_2$	67·61	5·73
3:4-$C_6H_3(OMe)_2$	84	165	yellow needles	67·72	5·86	do	67·61	5·73
3:4-C_6H_3(OEt)(OMe)	60	152	pale yellow needles	68·41	6·34	$C_{17}H_{18}O_3N_2$	68·46	6·09
2:3-C_6H_3(OH)(OMe)	81	168	red needles	66·55	5·36	$C_{15}H_{14}O_3N_2$	66·67	5·19
o-$C_6H_4(NO_2)$	86	174	yellow needles	62·48	4·17	$C_{14}H_{11}O_4N_3$	62·45	4·09
m-$C_6H_4(NO_2)$	95	199	yellow prisms	62·56	4·26	do	do	do
p-$C_6H_4(NO_2)$	93	191	yellow prisms	62·38	4·17	do	do	do
Ph·CH:CH	90	210	white needles	N,11·29		$C_{16}H_{14}ON_2$	N,11·20	
2:3:4-$C_6H_2(CO_2H)(OMe)_2$	96	208	white needles	62·15	5·14	$C_{17}H_{16}O_5N_2$	62·19	4·88

N^2-(2-Hydroxy-4-ethoxy-benzylidene) orthanilamide (a), N^2-(3-hydroxy-4-methoxy-benzylidene) orthanilamide (b), N^2-(3-ethoxy-4-hydroxy-benzylidene) orthanilamide (c) isomerise during recrystallisation from ethanol to the corresponding 4-oxoquinazolines. For identification and analysis (a) was ethylated and converted into 1:2:3:4-tetrahydro-2-(2′:4′-diethoxyphenyl)-4-oxoquinazoline, (b) and (c) were methylated and converted into 1:2:3-tetrahydro-2-(3′:4′-dimethoxyphenyl)-4-oxoquinazoline and 1:2:3:4-tetrahydro-2-(3-ethoxy-4-methoxy-phenyl)-4-oxoquinazoline respectively.

All compounds in Table 1 are new.

Table 2 summarises the results of isomerisation of arylideneorthanilamides by acid, alkali and heating. The numbers in parentheses indicate the percentage conversion to 1:2:3:4-tetrahydro-2-aryl-4-oxoquinazoline. Hy indicates hydrolysis.

Oxidation of 1:2:3:4-*tetrahydro*-2-*aryl*-4-*oxoquinazolines to* 2-*aryl-quinazol*-4-*ones*. The 4-oxoquinazoline dissolved in dry acetone was treated with potassium permanganate in dry acetone, which was added during 2–3 hours. Excess potassium permanganate was removed by addition of solid sodium bisulphite and the mixture filtered, and after evaporation of the acetone the residue consisting of the quinazol-4-one was recrystallised from ethanol or methanol. Table 4 gives details of the compounds prepared.

Table 2

	Acid	Alkali	Heat
Arylideneorthanilamide from			
o-hydroxy-benzaldehyde	(82) Hy	—	decomp.
o-methoxy-benzaldehyde	Hy	(88)	—
m-hydroxy-benzaldehyde	Hy	(100)	—
p-hydroxy-benzaldehyde	(70) Hy	—	—
p-methoxy-benzaldehyde	(62)	—	—
2-hydroxy-3-methoxy-benzaldehyde	(87) Hy	—	—
3-methoxy-4-hydroxy-benzaldehyde	(92) Hy	—	—
3:4-dimethoxy-benzaldehyde	Hy	(100)	—
4-methoxy-3-hydroxy-benzaldehyde	Hy	(100)	—
3-ethoxy-4-hydroxy-benzaldehyde	—	(100)	—
2-hydroxy-4-ethoxy-benzaldehyde	—	—	(100)
2:4-dimethoxy-benzaldehyde	Hy	(100)	—
2:4-diethoxy-benzaldehyde	Hy	(94)	—
3-ethoxy-4-methoxy-benzaldehyde	Hy	(80)	—
o-nitro-benzaldehyde	Hy	(96)	—
m-nitro-benzaldehyde	—	—	(96)
p-nitro-benzaldehyde	—	—	(90)
opianic acid	—	(100)	(100)
cinnamaldehyde	Hy	(58)	—

Footnotes to Table 3.

[a] Also obtained by methylating 1:2:3:4-tetrahydro-2-*p*-hydroxyphenyl-4-oxoquinazoline.

[b] Prepared by ethylating (i) N^2-(2′-ethoxy-4′-hydroxybenzylidene)orthanilamide; (ii) N^2-(2′-hydroxy-4′-ethoxybenzylidene)orthanilamide.

[c] N^2-(2′-hydroxy-3′-methoxyphenyl)orthanilamide could not be isomerised satisfactorily to the corresponding 4-oxoquinazoline by the action of sodium hydroxide or hydrochloric acid. The orthanilamide was refluxed in glacial acetic acid for ½ hr and the 4-oxoquinazoline precipitated by the addition of water, filtered, and crystallized from ethanol.

[d] was obtained by isomerisation of N^2-(3′-methoxy-4′-hydroxyphenyl)orthanilamide in glacial acetic acid, as in (c).

[e] Prepared by (i) methylating 1:2:3:4-tetrahydro-2-(3′-ethoxy-4′-hydroxyphenyl)-4-oxoquinazoline; (ii) ethylating 1:2:3:4-tetrahydro-2-(3′-hydroxy-4′-methoxyphenyl)-4-oxoquinazoline.

[f] was obtained by methylating (i) 1:2:3:4-tetrahydro-2-(3′-methoxy-4-hydroxyphenyl)-4-oxoquinazoline; (ii) 1:2:3:4-tetrahydro-2-(3′-hydroxy-4′-methoxyphenyl)-4-oxoquinazoline; (iii) N^2-(3′-methoxy-4′-hydroxybenzylidene)othanilamide; (iv) N^2-(3′-hydroxy-4′-methoxybenzylidene)orthanilamide.

[g] 1:2:3:4-tetrahydro-(*o*-nitrophenyl)-4-oxoquinazoline was also obtained by refluxing N^2-2-(*o*-nitrobenzylidene)orthanilamide (10 g) in water (50 c.c.) and ethanol (25 c.c.) and saturated sodium hydrogen carbonate solution (5 c.c.) for 1 hr. The 4-oxoquinazoline was deposited on cooling in ice, filtered, and crystallised from ethanol.

[h] Also prepared by refluxing cinnamaldehyde (3 g) and anthranilamide (3 g) in ethanol in presence of a flake of sodium hydroxide. The 4-oxoquinazoline separates as yellow plates or needles on cooling.

[i] 1:2:3:4-tetrahydro-2-(3′:4′-methylenedioxyphenyl)-4-oxoquinazoline was also prepared by allowing a mixture of piperonal (3 g) and methyl anthranilate (3 g) in ethanol to remain for 2 days at room temperature and then saturating with ammonia. After 4 weeks, concentrated aqueous ammonia was added and the precipitated compound was crystallised from methanol in white needles, m.p. 202°.

Ethylation and methylation were done at 0° in alkaline solution using ethyl and methyl sulphate respectively.

All compounds in Table 3 are new.

Methyl N-(α-*hydroxybenzyl*)*orthanilate* (XI). Methyl anthranilate (15·1 g) and benzaldehyde (10·6 g) were mixed in light petroleum (60–80°) and kept in an atmosphere of carbon dioxide in a refrigerator for 3 days. The addition product separated as a white solid (75%) which crystallised in needles from light petroleum (40–60°), m.p. 77° (Found: C, 70·44; H, 5·7. $C_{15}H_{15}O_3N$ requires C, 70·02; H, 5·88%). Methyl *N*-(α-hydroxy-4-methylbenzylorthanilate (XIII) was similarly prepared (65%) by addition of methyl anthranilate and *p*-methyl-benzaldehyde, crystallised in white needles, m.p. 79° (Found: C, 71·44; H, 6·16. $C_{16}H_{17}O_3N$ requires C, 70·85; H, 6·27%). Treatment of the above compounds in ethanol saturated with ammonia gave, respectively (after remaining in the refrigerator for two weeks), 1:2:3:4-tetrahydro-2-phenyl-4-oxoquinazoline (XII) (41%), m.p. 228°, and 1:2:3:4-tetrahydro-2-*p*-totyl-4-oxoquinazoline (XIV) (58%), m.p. 230°, identical in both cases with the compounds previously prepared (Table 3).

TABLE 3.—1:2:3:4-TETRAHYDRO-2-ARYL-4-OXOQUINAZOLINES
(For yields see Table 2)

Aryl	m.p.	Form	Solvent	Found (%)		Formula	Required (%)	
				C	H		C	H
Ph	228°	white needles	MeOH	75·34	5·6	$C_{14}H_{12}ON_2$	75·0	5·36
p-MeC_6H_4	230°	rhombic prisms	MeOH	75·58	6·0	$C_{15}H_{14}ON_2$	75·63	5·98
o-$C_6H_4(OH)$	300°	white needles	EtOH	69·75	5·16	$C_{14}H_{12}O_2N_2$	70·0	5·0
m-$C_6H_4(OH)$	209°	white needles	MeOH	69·76	5·21	$C_{14}H_{12}O_2N_2$	70·0	5·0
p-$C_6H_4(OH)$	332°	white needles	EtOH	—	—	—	—	—
o-$C_6H_4(OMe)$	181°	white needles	EtOH	70·75	5·68	$C_{15}H_{14}O_2N_2$	70·87	5·51
p-$C_6H_4(OMe)$[a]	195°	white needles	MeOH	70·96	5·7	$C_{15}H_{14}O_2N_2$	70·87	5·51
2′:4′-$C_6H_3(OH)$-(OEt)	305°	white needles	EtOH					
2′:4′$C_6H_3(OEt)_2$[b]	149°	white needles	EtOH	69·01	6·63	$C_{18}H_{20}O_3N_2$	69·23	6·46
2′:4′-$C_6H_3(OMe)_2$	187°	white needles	EtOH	65·29	6·47	$C_{16}H_{16}O_3N_2$ + EtOH.	65·45	6·6
2′:3′-C_6H_3(OH)(OMe)[c]	279°	yellow needles	AcOH	N, 10·4%		$C_{15}H_{14}O_2N_2$	N, 10·37%	
3′:4-C_6H_3(OMe)(OH)[d]	224°	white needles	EtOH					
3′:4′-C_6H_3(OH)(OMe)	191°	white needles	EtOH					
3′:4′-C_6H_3(OEt)(OMe)[e]	89°	white needles	EtOH	68·31	6·21	$C_{17}H_{18}O_3N_2$	68·46	6·04
3′:4′-C_6H_3(OEt)(OH)	218°	white needles	EtOH					
3′:4′-C_6H_3-$(OMe)_2$[f]	226°	white needles	AcOH	67·66	5·86	$C_{16}H_{16}O_3N_2$	67·61	5·73
o-$C_6H_4NO_2$[g]	192°	yellow needles	EtOH	62·50	4·12	$C_{14}H_{11}O_3N_3$	62·45	4·09
C_6H_5-CH:CH[h]	294°	yellow prisms	EtOH	N, 11·11%		$C_{16}H_{14}ON_2$	N, 11·2%	
3′:4′-$C_6H_3(CH_2O_2)$[i]	202°	white needles	MeOH	67·64	4·72	$C_{15}H_{12}O_3N_2$	67·17	4·48
2′:3′:4′-$C_6H_2(CO_2H)(OMe)_2$	296°	white needles	EtOH	N, 8·54%		$C_{17}H_{16}O_5N_2$	N, 8·54%	

Reaction between methyl anthranilate and benzaldehyde in presence of hydrogen chloride. A solution of methyl anthranilate (10 g, 2 mol) and benzaldehyde (4 g, 1·1 mol) in ethanol (50 c.c.) was warmed with a trace of hydrogen chloride. The solution became orange in colour, and after refluxing for 40 min a white crystalline solid separated which was filtered hot (8·6 g), m.p. 265–275°. Extraction with acetone yielded an insoluble portion (6·9 g), m.p. 278–280° (Found: C, 73·68; H, 5·35. $C_{22}H_{18}O_3N_2$ requires C, 73·72; H, 5·06%, which corresponds with (X)). Evaporation of the acetone solution left a residue (1·7 g), m.p. 188–190° (Found: C, 70·46; H, 5·71. $C_{23}H_{22}O_4N_2$ requires C, 70·77; H, 5·64%, which corresponds with (IX)).

During the present investigation the following new arylidene orthanilic acids were prepared:

TABLE 4.—2-ARYLQUINAZOL-4-ONES PRODUCED BY OXIDATION OF 1:2:3:4—TETRAHYDRO-2-ARYL-4-OXOQUINAZOLINES

Aryl	Yield (%)	m.p.	Form	Solvent	Found (%)			Formula	Required (%)		
					C	H	N		C	H	N
Ph*	70	238°	white needles	AcOH	—	—	—	—	—	—	—
p-C_6H_4·Me*	73	241°	"	acetone	—	—	—	—	—	—	—
o-C_6H_4·OMe	50	208°	"	EtOH	—	—	11·32	$C_{15}H_{12}O_2N_2$	—	—	11·11
p-C_6H_4·OMe*	98	247°	"	"	—	—	—	—	—	—	—
o-C_6H_4·NO_2	95	237°	yellow needles	EtOH	—	—	15·7	$C_{14}H_9O_3N_3$	—	—	15·74
m-C_6H_4·NO_2	96	354°d	"	AcOH	—	—	15·73	$C_{14}H_9O_3N_3$	—	—	15·74
p-C_6H_4·NO_2	90	365°d	white needles	AcOH	—	—	15·74	$C_{14}H_9O_3N_3$	—	—	15·74
2':4'-$C_6H_3(OMe)_2$*	75	207°	"	AcOH	67·8	5·17	—	$C_{16}H_{14}O_3N_2$	68·08	5·01	—
2':4'-$C_6H_3(OEt)_2$	87	174°	"	EtOH	69·7	6·06	—	$C_{18}H_{18}O_3N_2$	69·68	5·86	—
3':4'-$C_6H_3(OMe)_2$*	65	247°	"	AcOH	—	—	—	—	—	—	—
3':4'-$C_6H_3(O_2H_2C)$	75	279°	"	AcOH	67·43	4·06		$C_{15}H_{10}O_3N_2$	67·67	3·79	—
3':4'-C_6H_3(OEt) (OMe)	90	239°	"	acetone	68·66	5·59		$C_{17}H_{16}O_3N_2$	68·92	5·45	—
Ph·CH:CH*	44	252°	"	EtOH	—	—	11·35	$C_{16}H_{12}ON_2$	—	—	11·36

* Stephen and Wadge *J. Chem. Soc.* 4420 (1956).

N-(*2-hydroxy-4-ethoxybenzylidene*)*orthanilic acid* was obtained by refluxing a solution of 2-hydroxy-4-ethoxy-benzaldehyde (12·5 g) and anthranilic acid (10·3 g) in ethanol. A copious yellow crystalline deposit (19·8 g, 92%) of the condensation product was obtained which crystallised in yellow needles from ethanol, m.p. 206° (Found: C, 67·05; H, 5·01. $C_{16}H_{15}O_4N$ requires C, 67·21; H, 5·26%).

N-(*2-ethoxy-4-hydroxybenzylidene*)*orthanilic acid.* 2-ethoxy-4-hydroxy-benzaldehyde (1·66 g) and anthranilic acid (1·37 g) were mixed and dissolved in ethanol. After refluxing for 20 min and cooling, the condensation product separated as yellow needles (2·8 g, 97%) m.p. 211°, decomp. (Found: C, 66·95; H, 5·49. $C_{16}H_{15}O_4N$ requires C, 67·21; H, 5·26%).

N-(*3-methoxy-2-hydroxybenzylidene*)*orthanilic acid* was prepared by refluxing anthranilic acid (6·85 g) and 2-hydroxy-3-methoxybenzaldehyde (7·6 g) in benzene (80 c.c.). The condensation product (10·92 g, 80%) was deposited and crystallised from ethanol as orange needles, m.p. 119° (Found: C, 66·74; H, 5·01. $C_{15}H_{13}O_4N$ requires C, 66·41; H, 4·83%). The above compounds did not yield tetrahydro-4-oxoquinazolines on treatment with ammonia.

Acknowledgements—The authors thank Dr. R. S. Cahn for advice in connection with the nomenclature adopted in this paper.

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Tetrahedron, 1957, Vol. 1, pp. 45–48. Pergamon Press Ltd., London

PHOSPHOROUS PENTOXIDE-PYRIDINE: A NEW COMBINATION FOR BISCHLER-NAPIERALSKI REACTION

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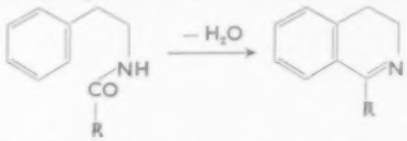
(*Received* 17 *August* 1956)

Abstract—The Bischler-Napieralski type of cyclisation can be effected by treating appropriately substituted acyl β-phenethylamides with phosphorous pentoxide in boiling pyridine. Isoquinolines can be recovered as the free base from the resultant pyridine layer; this reaction gives a good yield.

THE usefulness of the Bischler-Napieralski reaction and its modifications[1] for the preparation of 3,4-dihydroisoquinoline derivatives by dehydrating acyl β-phenethylamides is well established. The methods of Pictet[2] and Mannich[3] for the synthesis of isoquinolines may also be regarded as the modified forms of this reaction.



Phosphoryl chloride, usually in combination with benzene hydrocarbons, is now most extensively used as the cyclisation agent in these reactions. For more drastic conditions, phosphorous pentoxide is recommended, usually with boiling xylene, while the same agent in boiling tetralin is considered the most powerful dehydrating combination[4] in this type of reaction. A combination of phosphoryl chloride-phosphorous pentoxide[5] is also used in some cases, but since phosphoryl chloride is more easily handled this would seem to be the main reason of its popularity.

In minor cases, thionyl chloride,[6] and phosphorous pentachloride in cold chloroform[7] are also used, the latter of which appears to have a special feature to effect the cyclisation when phosphoryl chloride and phosphorous pentoxide are ineffective.[8] Polyphosphoric acid[9] will also be mentioned as a new reagent to be used for the same cyclisation purpose.

With all these reagents or reagent combinations the ring closure proceeds in acidic condition from the beginning to the end of the reaction, and thus the cyclisation of amide possessing any acid-sensitive group might suffer from some change either during the reaction or during the working up of the product. Thus, according to the

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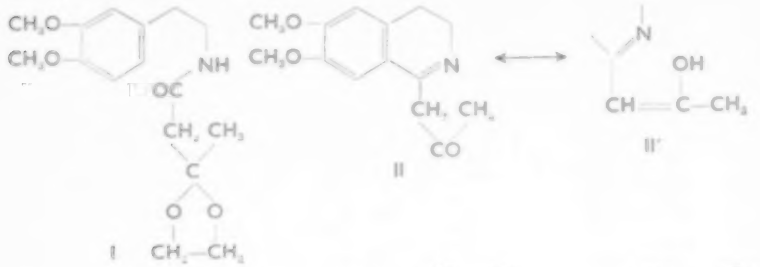
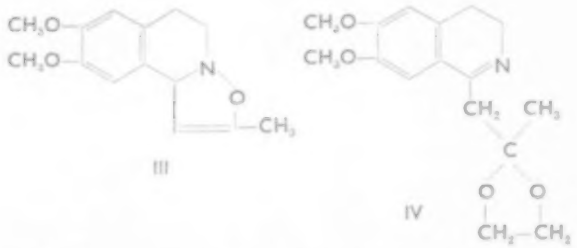
writers' experiments, the cyclisation of β-3,4-dimethoxyphenethyl-β-ethylenedioxybutyramide (I) by means of phosphoryl chloride in boiling benzene gave always an isoxazoline derivative (III) rather than the expected (IV). The former was probably produced by a prototropic change of 1-acetonylisoquinoline derivative (II) in its enolic form (II′), the hydrolysis product of (IV) by the agency of acid formed during the cyclisation reaction.*





In connection with a synthesis now being carried out in our laboratory, we hoped to find a new combination for the Bischler-Napieralski reaction, which allows the cyclisation to take place in a basic medium as a whole. For that purpose, two types of combination (i) phosphoryl chloride-pyridine and (ii) phosphorous pentoxide-pyridine were examined, of which the latter seemed preferable. Since phosphorous pentoxide itself is rather inconvenient to handle, it was mixed with inert material such as purified sea-sand, coarsely powdered limestone, or alumina.

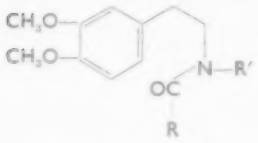
Some preliminary experiments carried out with this new combination, in which sea-sand only was used as the diluent for phosphorous pentoxide with satisfactory results, are described in this paper.

When β-(3,4-dimethoxyphenethyl)-acetamide (V) was treated with a mixture of phosphorous pentoxide and sand in boiling pyridine, 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (VI) was recovered in a good yield from the supernatant pyridine layer, which also contained some of the starting amide. From the pyridine washing of the caked residue practically none of the product was recovered, showing that all the product existed in the pyridine layer as the free base. The corresponding benzamide (VII) also gave a comparable result. Both isoquinolines (VI) and (VIII) were identified with the authentic specimens.

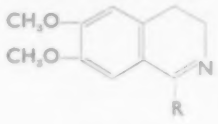
The cyclisation of β-(3,4-dimethoxyphenethyl)-benzyl-acetamide (IX) by this means is probably worth noting. From the resultant pyridine layer a yellowish oil was recovered, which was fairly unstable, turning reddish on exposure to air. The presence of 6,7-dimethoxy-1-methylene-2-benzyl-1,2,3,4-tetrahydroisoquinoline (X)

* The details of this experiment will be published in the forthcoming paper.

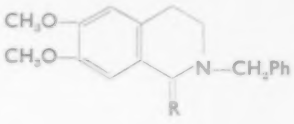
in this oil was established (i) by treating the oil with hydrochloric acid in the presence of potassium iodide, giving the stable quaternary benzyl iodide (XI), and (ii) by oxidising the oil with potassium permanganate in pyridine solution, furnishing *N*-benzylcorydaldin (XII). Direct oxidation of the pyridine layer of the reaction mixture also gave the same product.



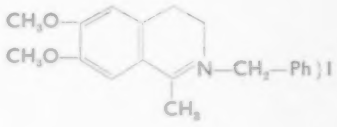
V: R = CH_3, R′ = H
VII: R = Ph, R′ = H
IX: R = CH_3, R′ = CH_2Ph



VI: R = CH_3
VIII: R = Ph



X: R = CH_2
XII: R = O



XI

The feature of this new combination exists in that, though the isoquinoline formation takes place on the surface of phosphorous pentoxide under acidic condition, the acid formed—probably metaphosphoric acid—will soon become neutralised with pyridine, liberating isoquinoline from the surface of the dehydrating agent, which then moves into the pyridine layer as a free base, and this will certainly be favourable for the synthesis of isoquinolines which contain any group sensitive to acid.

Application of this new combination to various other types of phenethylamides is now under progress, and the results will be the subject of further communications.

EXPERIMENTAL

6,7-*Dimethoxy*-1-*methyl*-3,4-*dihydroisoquinoline* (VI). This is described in detail as a general procedure. 3,4-(β-Dimethoxyphenethyl)-acetamide (V: 0·5 g) in pure pyridine (30 c.c.) was kept under gentle boiling, and to this solution was added an intimate mixture of phosphorous pentoxide (5 g) and dry sand (50 g) in four portions with stirring. Some time later, stirring became impossible due to caking of the dehydrating agent. After being refluxed for 6 hours, the dark-coloured pyridine layer was decanted and the residue extracted with 3 × 10-c.c. portions of hot pyridine. From the combined pyridine solution the solvent was removed *in vacuo*, leaving yellowish syrup (0·5 g), which was dissolved in benzene. The benzene solution was repeatedly extracted with dilute hydrochloric acid, and the combined acid solution was basified and salted out. The liberated base was collected in benzene, dried and evaporated, giving a faint yellow syrup (0·45 g) which solidified on standing. When purified from *n*-hexane, it formed colourless prisms of m.p. 108–109°, which was not depressed on admixture with an authentic specimen. The yield was 0·38 g, or *c.* 85% of the pure product.

From the original benzene solution a small amount of the starting amide was recovered.

The melting-points of the hydrochloride (199–200°) and of the picrate (210–212°) were also the same as recorded by previous workers.

6,7-*Dimethoxy*-1-*phenyl*-3,4-*dihydroisoquinoline* (VIII) forms colourless prisms from ethyl acetate; its melting-point of 120° was not depressed when admixed with an authentic sample. It gave a yield of 0·3 g, or *c.* 83% from 0·35 g of the starting amide.

6,7-*Dimethoxy*-1-*methylene*-2-*benzyl*-1,2,3,4-*tetrahydroisoquinoline* (X). The cyclisation of the amide (IX) was carried out as above. When pyridine was removed *in vacuo*, there remained a yellowish brown viscous oil, which could not be purified because of its unstable nature in air and was directly converted into the quaternary salt.

6,7-*Dimethoxy*-1-*methyl*-2-*benzyl*-3,4-*dihydroisoquinolinium iodide* (XI). The above-mentioned oil was treated with hydrochloric acid added with sufficient amount of potassium iodide; the yellowish solid which was separated was purified from alcohol, and formed stable yellow needles of m.p. 183–184°, being identified by mixture melting-point test with an authentic sample prepared from the compound (VI), benzyl chloride and potassium iodide. Thus, 0·41 g of the pure iodide (XI) was obtained from 0·5 g of the amide (IX), yield *c.* 76%.

Oxidation of 6,7-*Dimethoxy*-1-*methylene*-2-*benzyl*-3,4-*dihydroisoquinoline* (X). (i) The crude base (X: 0·2 g), obtained as above, in pure pyridine (30 c.c.), was oxidised by adding an aqueous potassium permanganate solution (made from 0·2 g of the oxidising agent and 30 c.c. of water) with stirring and cooling in the running water. After about 2 hours stirring, the unreacted permanganate was decomposed by adding enough methanol, filtered from manganese dioxide, and the filtrate was evaporated *in vacuo*, yielding a colourless glass, which solidified on standing. Purified from *n*-hexane, the benzylcorydaldin thus obtained formed colourless prisms of m.p. 84°, which was not depressed on admixture with an authentic specimen prepared as shown below. The yield was 0·2 g, which is nearly the theoretical value (Found: C, 72·8; H, 6·1; N, 4·9. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4; N, 4·7).

(ii) The direct oxidation of the pyridine solution gave the same compound. Thus, the amide (IX: 0·3 g) was cyclised in boiling pyridine as already stated. The pyridine layer was decanted from the caked residue and was directly treated with an aqueous solution of potassium permanganate (0·3 g in 30 c.c. of water) and treated as previously described. The residue was dissolved in a mixture of benzene and *n*-hexane (100 c.c. each), purified through an alumina column, and the solvent was removed by distillation. The residue was purified from *n*-hexane, giving 0·18 g of pure benzylcorydaldin of m.p. 84°, which remained unchanged when admixed with an authentic sample.

An authentic N-*benzylcorydaldin*. 6,7-Dimethoxy-3,4-dihydro-*N*-benzylisoquinolinium chloride (1 g) in *c.* 10 c.c. of water was oxidised by adding an alkaline potassium ferricyanide solution (8 g of ferricyanide in 60 c.c. of 10% sodium hydroxide solution) with stirring and water-cooling for a period of half an hour; stirring was continued for an additional half-hour. The filtrate was repeatedly extracted with ether, dried, and evaporated, leaving a yellowish solid, which was purified from *n*-hexane, forming colourless prisms of m.p. 84°, giving a yield of 0·8 g, or *c.* 86% of the pure product (Found: C, 72·9; H, 6·3. $C_{18}H_{19}O_3N$ requires C, 72·7; H, 6·4).

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Tetrahedron, 1957, Vol. 1, pp. 49–66. Pergamon Press Ltd., London

STEROIDS AND RELATED COMPOUNDS—I

SYNTHESIS OF 1:2:3:4:9:10:11"β":12"α"-OCTAHYDRO-7-METHOXY-2"α":8:11"β"-TRIMETHYL-3-OXOPHENANTHRENE

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(*Received* 25 *January* 1957)

Abstract—Starting with 6-methoxy-5-methyltetralin (I), several routes to the compound (XXI) named in the title have been developed. The tetralin (I) was converted into the hexahydrophenanthrene (X) and some attempts were made to convert the latter into a 2:3-glycol or related compound with a view to changing the potential homo-*D*-ring into a natural *D*-ring before reducing the 4:12-double bond. The ketone (X) was converted into the desired product (XXI) by a three-stage methylation and one-, two-, or three-stage reductions, the order of the reactions being varied to achieve structural and steric specificity. When attempting to predict and later to rationalise the steric course of the reductions, it was found that the concept of catalyst hindrance[1] provided a better guide than Hadler's conformational arguments which were originally applied to Δ^4- and Δ^5-steroids.[2]

IN several steroid syntheses a homo-*D*-ring has been built up at an early stage and later converted into a five-membered ring. In this way, advantage can be taken of the better understanding of the stereochemistry of polycyclic *cyclo*hexane derivatives, but this is worth while only if the 6-membered-*D*-ring is easily fabricated and changed into a suitably substituted 5-membered-*D*-ring. In previous syntheses such *homo-D*-rings have come from phenolic aromatic rings (as in 1:6-dihydroxynaphthalene[3] and 2-methylresorcinol[4]) and by diene synthesis,[5] but the use of the "ring extension" method (or an equivalent series of reactions) has been surprisingly neglected. The value of using a naphthalene derivative for the *B*- and *C*-rings has been shown clearly[6,7] and if a 2-methyl-1-tetralone such as (VI) were to be ring-extended, the resulting unsaturated ketone, such as (X), provides (a) several possibilities for reduction to a *C/D-trans*-fused ring system, which is itself a part of the natural steroid structure and leads to stereospecific reduction at a later stage[7] (b) the possibility of introducing a carbon atom at $C_{(2)}$ and (c) the functional group needed for transforming the *homo-D*-ring. Apart from some exploratory experiments,[8] only Stork, Loewenthal, and Mukharji[9] and the present author have used this approach, in almost identical ways.

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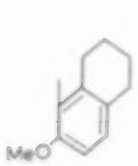
[5] R. B. Woodward, F. Sondheimer, D. Taub, K. Heussler and W. M. McLamore *J. Amer. Chem. Soc.* **74**, 4223 (1952).
[6] H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann, and Sir R. Robinson *J. Chem. Soc.* 361 (1953).
[7] J. W. Cornforth, O. Kauder, J. E. Pike, and Sir R. Robinson *ibid.* 3348 (1956).
[8] A. R. Pinder and Sir R. Robinson *ibid.* 3341 (1955).
[9] G. Stork, H. J. E. Loewenthal, and P. L. Mukharji *J. Amer. Chem. Soc.* **78**, 501 (1956).

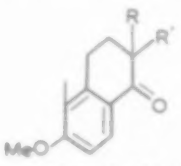
The reactions considered suitable for opening the *D*-ring between $C_{(2)}$ and $C_{(3)}$ depended upon enolisation of a 3-carbonyl group or elimination of a suitable 3-substituent with formation of a 2:3- rather than a 3:4-double bond. This mode of reaction was expected to predominate particularly if the *C*- and *D*-rings were *trans*-fused, but we hope to give a fuller discussion of this point elsewhere.

We had originally intended to use 6-methoxy-1-tetralone as the starting material (cf. ref. 9), since the reduction of polycyclic aromatic ethers related to 6-methoxytetralin had already been accomplished and the $C_{(18)}$* methyl group could be added after the $C_{(1)}$-$C_{(2)}$* part of the *A*-ring, thereby obtaining predominantely axial methylation (this steric control has been realised[10] in a development of Woodward's steroid synthesis). The availability of a supply of 6-methoxy-2-methoxycarbonyl-2:5-dimethyl-1-tetralone (V) and 6-methoxy-5-methyltetralin (I), and the misleading observation that the latter is readily reduced to 1-methyl-$\Delta^{1(9)}$-octal-2-one (II) led us to study a route parallel to, rather than identical with, that followed by Stork, Loewenthal, and Mukharji. In both series of reactions the intermediate 2-methyl-1-tetralone (such as VI) has only one active hydrogen atom and a single racemic product can result from a "ring extension," and a convenient preparation of the ketone (X) was the first objective.

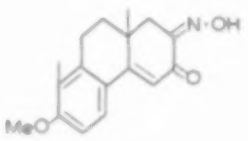
The preparation of the tetralone (VI) from 6-methoxy-5-methyltetralin (I) has been improved and shortened. The methoxycarbonylation and methylation of the tetralone (III) has been carried out without isolation of the intermediate ester (IV), previously prepared by glyoxylation and pyrolytic loss of carbon monoxide.[11] Use was made of filtration through short columns of alumina, using relatively concentrated



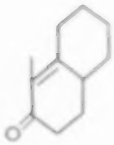
(I)



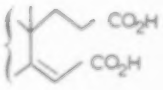
(III) R = R' = H
(IV) R = CO_2Me, R' = H
(V) R = CO_2Me, R' = Me
(VI) R = Me, R' = H
(VII) R = Me, R' = $(CH_2)_2CN$
(VIII) R = Me, R' = $(CH_2)_2CO_2H$
(IX) R = Me, R' = $(CH_2)_2CO_2Me$



(XV)



(II)



(XVI)

solutions, instead of distillation in the purification of intermediates. The condensation of the tetralone (VI) with diethylmethyl-(3-oxobutyl)-ammonium iodide was unpromising, and although the ketone (X) was isolated in low yield, this method was not developed. Instead, the tetralone (VI) was cyano-ethylated in *t*-butanol and the resulting nitrile (VII) was hydrolysed to the acid (VIII) and the latter was esterified, giving the methyl ester (IX) (yield *c.* 87% from VI). Under forcing conditions this

* Steroid numbering.

[10] L. B. Barkley, W. J. Knowles, H. Raffelson, and Q. E. Thompson *ibid.* 4111.

[11] R. H. Martin and Sir R. Robinson *J. Chem. Soc.* 491 (1943).

ester reacted with methyl acetate and sodium methoxide and the whole product was boiled with formic acid, giving the phenanthrene derivative (X) (*c.* 70% yield from the tetralone VI). The sodium salts present buffered the mixture sufficiently to prevent decomposition of the ketone (X), which is sensitive to strong acids, including hot concentrated formic acid. The ketone (X) and compounds containing the same chromophore, and the corresponding alcohols, such as (XXVIII), give a variety of colour reactions with acidic reagents which were useful for detecting these compounds, particularly near the end of reductions (see Table 1 and below).

TABLE 1.—COLOUR REACTIONS GIVEN BY SOME OF THE COMPOUNDS PREPARED IN THIS WORK. THE SOLUTION USED FOR THE MODIFIED LIEBERMANN TEST WAS A FRESHLY PREPARED MIXTURE OF ACETIC ANHYDRIDE AND SULPHURIC ACID (12:1)

Compound	Colour in formic acid	Liebermann test	
		Cold	Heated to boiling and cooled
X	yellow, w	yellow,	cherry
XIV	(y-green, w)*	(y-green, s)	(green, s)
X†	—	yellow, s (green, w)	red-brown
XV	—	orange	orange (y-green)
XI	y-green (green, s)	orange, s (green)	crimson, s (red)
XII	pale yellow	yellow	yellow
XIII	(y-green, w)		
XXVIII	yellow, changing to blue at the boiling-point.	orange	red
XXX	yellow, changing to blue-green at the boiling-point	orange	red

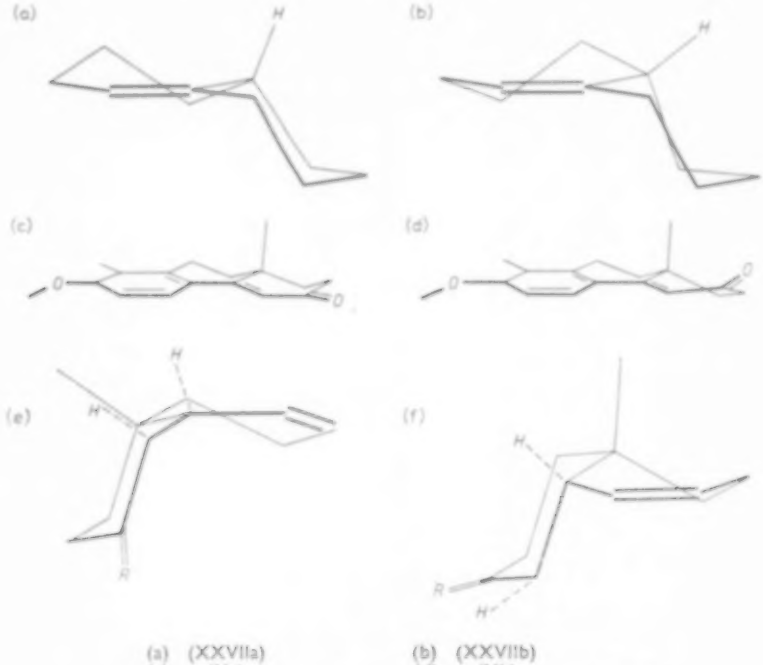
* Colours of fluorescences are enclosed in brackets; intensities are only indicated when they are strong (s) or weak (w).
† Semicarbazone of the ketone (X).
y-green = yellowish green.

Although only racemates were prepared, the 11-methyl group in the ketone (X) will by convention be taken to be "β"-oriented* (and above the mean plane of the molecule) to facilitate the naming of stereoisomers and to indicate relationships with the natural steroids. It seems very probable that the ketone (X) has the *C*- and *D*-rings in the half-chair conformation,[12] since (a) that is the more stable for *cyclo*hexene (b) allows the molecule to be nearly strain-free, judging from models, and (c) the conjugated system is planar and therefore the resonance stabilisation should be maximal.

*Previous authors, e.g. ref. 7, have used heavy and broken lines in formulae, and Greek letters in inverted commas in names, to denote *relative* configurations of racemic compounds. This convention will be followed in this paper.

[12] C. W. Beckett, N. K. Freeman, and K. S. Pitzer *J. Amer. Chem. Soc.* **70,** 4227 (1948); D. H. R. Barton, R. C. Cookson, W. Klyne, and C. W. Shoppee *Chem. and Ind.* **21,** (1954).

In this conformation (see Xa) only the 11-methyl group is above and the 1- and 10-methylene groups are below the mean plane of the molecule. It seems that the ketone (X) is much more stable in the conformation (Xa) than (Xb), since compounds with two large substituents at $C_{(2)}$ show the same ultra-violet absorption spectra as the unsubstituted ketone (X), in spite of the interference between the axial 11"β"- and 2"β"-substituents which would not be present in the conformation (Xb), in which the *D*-ring is in the half-boat form, but this difference in stability is probably reduced considerably in the transition states for reduction of the $\Delta^{4:12}$ double bond or the carbonyl group (see below). Models of the ketone (X) with the *C*-ring in a half-boat form were very strained and were not considered further.



(a) (XXVIIa) (b) (XXVIIb)
(c) (Xa) (d) (Xb)
(e) (XXIIa) R = O (f) (XXIIb) R = O

(XXXIIa) R = H, OH (XXXIIb) R = H, OH

(In (e) and (f) the aromatic ring is omitted except for the (double) bond common to rings *B* and *C*, and only the two hydrogen atoms added during reduction of the 4:12-double bond are shown.)

Fig. 1.—Conformations of $\Delta^{1(9)}$-octalin (XXVII), the ketones (X) and (XXII), and the alcohol (XXXII).

Some attempts were made to introduce an oxygen function at $C_{(2)}$ in the ketone (X) with a view to preparing a 2:3-glycol (cf. ref. 5) before reduction of the double bond. The purpose was to make use of the undirectional enolisation of the ketone (X), although it was recognised that the *trans-C/D* ketones (XVII) and (XXI) should react predominantely at $C_{(2)}$. The ketone (X) gave intractable tars when treated with

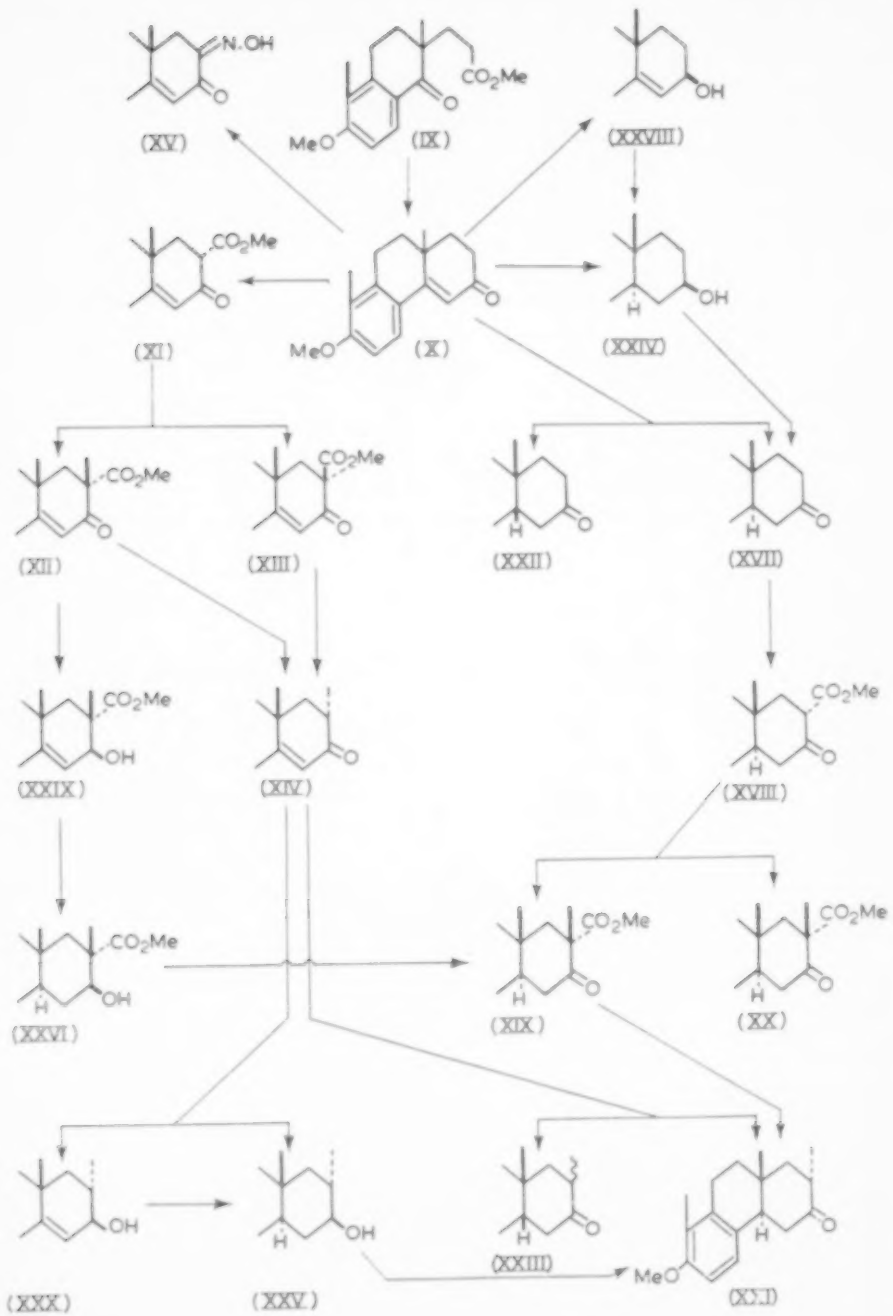
selenium dioxide in ethanol, acetic acid, or acetic anhydride, and with lead tetra-acetate in acetic acid. With bromine in acetic acid the ketone (X) gave green tars, but in the presence of sodium acetate a bromoderivative (probably the 6-bromoketone, because the bromine atom was unreactive and the 6-position is *ortho* to the methoxyl group) was formed. This bromoketone was not sensitive to acids, but further acid-catalysed bromination was not successful. In the presence of sodium acetate, further bromination gave moderate yields of a di- and (impure) tri-bromoketone. Part of the bromine in the latter reacted with sodium acetate, but no acetoxydibromoketone was obtained from this reaction or from the bromination mixture. The most promising approach was nitrosation of the ketone (X) with *t*-butyl nitrite and potassium *t*-butoxide,[13] but the resulting α-oximinoketone (XV) could not be hydrolysed, and the method of reductive hydrolysis applicable to some α-oximino*cyclo*pentanones[14] brought about reduction to a very unstable basic substance, presumably an aminoketone. A similar product was obtained by catalytic reduction, but neither could be purified either as the base or as the hydrochloride.

In the main synthetic route the methylation of the ketone (X) was the next objective. From the methoxycarbonylation of the ketone (X) the β-oxoester (XI) could be isolated in nearly quantitative yield, provided the reaction was forced to completion by removing methanol as it was formed, but the β-oxoester (XI) was conveniently methylated without isolation, forming mainly the 2"β"-methyl derivative (XII) and some of the isomer (XIII). Both the esters (XII) and (XIII) were hydrolysed by alkali to (XIV) (*c.* 80% from X), without any of the expected dibasic acid (XVI). In one experiment, using a shortened reaction time, the sodium salt corresponding to the ester (XII) was isolated as a by-product. The structures of the esters (XII) and (XIII) will be discussed below.

Several methods were tried for the reduction of the ketones (X) and (XIV) to the *trans*octahydrophenanthrenes (XVII) and (XXI). Lithium in liquid ammonia was used first, because this was known to give thermodynamically more stable products[15] in general, and *trans*octahydrophenanthrenes in particular,[7] although the effect of the different positions of the functional groups was not known. The reaction was much slower with the ketones (X) and (XIV) and gave mixtures of *cis* and *trans* ketones, (XVII and XXII) and (XXI and XXIII) respectively, which could not be separated directly by crystallisation, and the mixtures were converted into methyl and ethylene ketals respectively. The ethylene ketals were prepared by a standard method,[17] but the methyl ketals were prepared by crystallising the mixed ketones (XVII) and (XXII) from boiling acidified methanol. Similar preparations of methyl ketals have been reported recently.[18] The ketals from the *trans* ketones (XVII) and (XXI) only were obtained crystalline (*c.* 50% yields), and these were hydrolysed to the pure ketones in acetone.[17] The *cis* ketones (XXII) and (XXIII) were obtained in low yields from the ketal residues.

Methoxycarbonylation of the ketone (XVII) gave exclusively the β-oxoester (XVIII), which on methylation gave mainly the derivative (XIX), and a very small

[13] F. Litvan and Sir R. Robinson *J. Chem. Soc.* 1997 (1938).
[14] L. Claisen and E. Manasse *Annalen* **274**, 90 (1893); F. H. Stodola, E. C. Kendall, and B. F. McKenzie, *J. Org. Chem.* **6**, 841 (1941); M. N. Huffman and M. H. Lott *J. Amer. Chem. Soc.* **76**, 4038 (1954).
[15] D. H. R. Barton and C. H. Robinson *J. Chem. Soc.* 3045 (1954).
[16] F. Sondheimer, O. Mancera, G. Rosenkrantz, and C. Djerassi *J. Amer. Chem. Soc.* **75**, 1282 (1942).
[17] G. I. Poos, G. E. Arth, G. E. Beyler, and L. H. Sarett *ibid.* 422.


N.OH
(XV)
MeO
CO2Me
(IX)
OH
(XXVIII)
CO2Me
(XI)
MeO
(X)
OH
H
(XXIV)
CO2Me
(XII)
CO2Me
(XIII)
H
(XXIII)
H
(XVII)
CO2Me
OH
(XXIX)
(XIV)
CO2Me
H
(XVIII)
CO2Me
H
OH
(XXVI)
CO2Me
H
(XIX)
CO2Me
H
(XX)
OH
(XXX)
H
OH
(XXV)
H
(XXIII)
MeO
H
(XXI)

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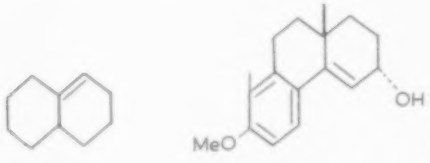
amount of a product thought to be (XX) (the structures are discussed below) and (XIX) was hydrolysed by acid or alkali to the ketone (XXI), identical with the main product from the lithium reduction of the ketone (XIV). This series of reactions (a) shows that the main products from the reductions of (X) and (XIV) belong to the same stereochemical series, (b) strongly supports the assignment of a *trans* configuration to the *C/D*-ring fusion, although the high yield of the β-oxoester (XVIII) may be due to the reversibility of methoxycarbonylation and low solubility of the sodium derivative of (XVIII), and (c) shows that the 2-methyl group in the ketone (XXI) is equatorial (i.e. α-oriented), because the conditions of the hydrolysis should suffice to ensure equilibration. The ketone (X) was also reduced with lithium and ethanol in liquid and from product the *ketones* (XVII) and (XXII) were isolated in low yield through a Girard separation and alcohol (XXIV) in up to 40% yield either directly or from the nonketonic fraction. The alcohol (XXIV) was oxidised by chromium trioxide in pyridine to the trans ketone (XVII) and the hydroxyl group was assigned the equatorial "β"-configuration on the basis of the method of formation.[15] It is interesting to note that the oxidation of the alcohol (XXIV) produced a small quantity of the *unsaturated* ketone (X). The oxidation of a similar alcohol to an unsaturated ketone by chromic acid has been reported,[19] but chromium trioxide in pyridine is usually regarded as very selective and not likely to give the variety of by-products commonly found with chromic acid in acidic solvents.

The lithium reductions described above were not suitable on a preparative scale because of the tedious separations and moderate overall yields, and catalytic hydrogenation was considered as an alternative. Although $\Delta^{1(9)}$-octalin (XXVII) and many related compounds give predominantly *cis*decalins[20] when reduced catalytically, some simple exceptions, as well as the more complex examples, such as cholesterol, are now known.[20,21] It has been suggested that catalyst hindrance[1] leads to reduction to a *trans*decalin when there are bulky groups (such as a 10-methoxycarbonyl group) hindering the normal reduction to a *cis*decalin,[20] but the basic cause of the tendency to give a *cis*decalin has only recently been discussed. Hadler[2] considered the steric

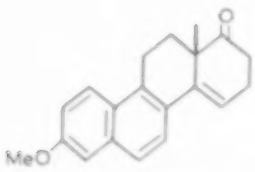


(XXVII) (XXXI) (XXXII)

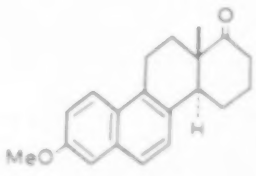
repulsions experienced by the two hydrogen atoms forming part of a 6-membered ring transition complex (two catalyst active sites, the two hydrogen atoms being added and the two carbon atoms of the original double bond), which was assumed to have the shape of the *product*. This approach clearly explains the course of the reduction of cholest-4- and 5-ene, and the influence of 3α- and 3β-substituents in the latter, but the

[18] E. P. Oliveto, C. Gerold, and E. B. Herschberg *ibid.* **76**, 6113 (1954); P. A. Robins and J. Walker *J. Chem. Soc.* 3260 (1956).
[19] V. Arkley, F. M. Dean, A. Robertson, and P. Sidisunthorn *ibid.* 2322.
[20] W. G. Dauben, R. C. Tweit, and R. L. MacLean *J. Amer. Chem. Soc.* **77**, 48 (1955).
[21] A. S. Dreiding and A. J. Tomasewski *ibid.* 411; M. Yanagita, K. Yamakawa, A. Tahara, and H. Ogura *J. Org. Chem.* **20**, 1767 (1955).

effect of a bulky angular group is underemphasised. From the alternative extreme viewpoint, Robinson[22] considered the hindrance offered to the two modes of adsorption of the molecule on the catalyst surface,[1] this being equivalent to assuming that the transition state has the same geometry as the *reactant*. Thus $\Delta^{1(9)}$-octalin is folded in both the possible conformations (XXVIIa) and (XXVIIb), and the adsorption of the open side of the molecule on the catalyst will lead to reduction to *cis*decalin. If a bulky angular group is present, approach to the double bond is less hindered in (XXVIIb), and this will be the favoured one for reduction. But in polycyclic compounds the conformation will be fixed, for example cholesterol corresponds to (XXVIIa), in which the $C_{(18)}$*-methyl group will be most hindering, thereby favouring adsorption of the other side of the molecule. When considering the reduction of the ketone (X) the problem is less simple, because the reduction cannot be stopped at the ketones (XVII) and (XXI) (see below), and there must be some doubt about which stage comes first. Furthermore, when using Hadler's approach both possible conformations (see Fig.) for the *cis*octahydrophenanthrenes, e.g. (XXIIa) and (XXIIb), which are presumably readily interconvertible, must be considered. If the 4:12-double bond is reduced first, catalyst hindrance will lead predominantly to the *trans*-ketone (XVII), because the 11-methyl group should be more effective than the $C_{(1)}$ and $C_{(10)}$ methylene groups, but following Hadler, the predicted yields are in the order (XXIIb)>(XVII)>(XXIIa). The second stage of the reduction should give mainly equatorial hydroxyl groups with the catalyst used. If the carbonyl group is reduced first, product stability and steric hindrance both favour the 3"β"-alcohol (XXVIII) slightly. This alcohol will be reduced specifically to the *trans*-3"β"-alcohol (XXIV) through catalyst hindrance, but not otherwise, and the less abundant 3"α"-alcohol (XXXI) will be reduced to the *cis*-3"α"-alcohol (XXXII) (in the conformation XXXIIb rather than XXXIIa) if Hadler is correct, but not specifically through hindrance. The overall result is that catalyst hindrance should lead mainly to *trans* products and, following Hadler, mainly *cis* products would be expected. Since the reduction of the ketone (X), the 3"β"-alcohol (XXVIII), and the ester (XII) gives a *trans* product and agrees with the recently reported[21] reduction of the ketone (XXXIII) to (XXXIV) (XXXIV having been converted into equilenin), catalyst hindrance appears to be the better guide.



(XXXIII)



(XXXIV)

When the ketone (X) was reduced catalytically, the alcohol (XXIV) was formed in 60% yield, with no evidence of a break in the slow hydrogen uptake corresponding to the ketone (XVII), and preliminary reduction of the carbonyl group to a 3"β"-hydroxyl was tried to improve the yield. It has been suggested that the ratio of the amounts of

*Steroid numbering.

[22] M. J. T. Robinson Thesis, Oxford, 1955.

[21] W. G. Dauben, E. J. Blanz, J. Jiu, and R. A. Micheli *J. Amer. Chem. Soc.* **78**, 3752 (1956).

[1] Cheng Chin *Scientia Sinica* **4**, 547 (1955).

epimeric alcohol formed by the metal borohydride reduction of a ketone is determined by a balance between steric hindrance to the approach of the reagent and the relative stabilities of the developing products,[23] the usual result being that the product contains more of the less stable epimer than the equilibrium mixture. Lithium aluminium hydride reduction of cholest-1-en-3-one gave 90% of cholest-1-en-3β-ol,[25] and 5-methyl*cyclo*hexen-3-one similarly gave 93% of *cis*-5-methyl*cyclo*hexen-3-ol, although the equilibrium amount is only 55% at 100°.[26] and there is no marked steric hindrance. The reductions of some 6-alkyl*cyclo*hexen-3-ones to *trans*-6-alkyl*cyclo*hexen-3-ols are qualitatively similar.[27] There is evidence, furthermore, that metal borohydrides are more stereospecific than lithium aluminium hydride,[23] and it seemed that the ketone (X) might be reduced specifically to the 3"β"-alcohol (XXVIII) by potassium borohydride. The alcohol (XXVIII) was obtained in 83–87% yield, but when it was reduced catalytically the reduction was complete when only 80% of the theoretical amount of hydrogen had been absorbed. The contaminant must have been the saturated alcohol (XXIV), since this was obtained quantitatively and nearly pure from this hydrogenation. The alcohols (XXIV) and (XXVIII) did not depress each other's melting-points very much and probably form a solid solution, since crystallisation of the latter did not raise or sharpen its melting-point, although it must have contained *c.* 20% of the alcohol (XXIV) to account for the hydrogenation. Metal borohydride reduction of double bonds conjugated with carbonyl groups has been reported.[28] The overall reduction was less specific when lithium aluminium hydride was used. Potassium borohydride reduction of the ketone (XIV) gave a mixture from which the alcohol (XXV), contaminated with about 15% of the unsaturated alcohol (XXX), was isolated in 30% yield. When this mixture was reduced catalytically, the pure alcohol (XXV) was obtained and the latter was oxidised to the ketone (XXI). With anhydrous formic acid the alcohols (XXVIII) and (XXX) gave intense orange colorations which changed slowly to blue. A similar slow change in acid solutions of some diarylethylenes has been attributed, somewhat improbably, to a change from a classical to a "π-complex" carbonium ion.[29]

Because the reduction of the ketone (XIV) was less simple than was the case with the ketone (X), the reduction of the esters (XII) and (XIII) was studied as a route to the ketone (XXI). These esters would be expected to be reduced to *trans* products provided the *homo-D*-ring remains in the half-chair conformation (as in XIIa and XIIIa). However, any reaction which reduces the conjugation in the transition state will decrease this stabilising effect and the reaction may be less specific. The esters (XII) and (XIII) were not hydrogenated under conditions effective with the ketone (X), but were slowly reduced by potassium borohydride. The products, e.g. (XXIX) from (XII), were mixtures which could not be separated by crystallisation and which probably contained some of the saturated alcohols such as (XXVI), obtained in 75% yield after hydrogenation. The overall reaction is less specific than for the ketone (X), but provides the best route to the ketone (XXI), since the oxidation of the ester (XXVI) to the ester (XIX), previously prepared by methylating (XVIII), and the subsequent hydrolysis to (XXI) were both nearly quantitative. As in the oxidation of the alcohol

[25] W. Bergmann, M. Kita, and D. J. Giancola *J. Amer. Chem. Soc.* **76**, 4974 (1954).
[26] H. L. Goering and J. P. Blanchard *ibid.* 5405.
[27] G. Stork and W. N. White *ibid.* **78**, 4604 (1956).
[28] F. Sondheimer, M. Velasco, E. Batres, and G. Rosenkrantz *Chem. and Ind.* 1482 (1954).
[29] A. G. Evans, N. Jones, P. M. S. Jones, and J. H. Thomas *J. Chem. Soc.* 2757 (1956).

(XXIV) some conjugated ketone, presumably (XII), was formed and a relatively long time was required (cf. ref. 17). The mixture of products obtained from the ester (XII) was not studied, because it did not offer a useful route to the ketone (XXI). The sequence I, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XXIX, XXVI, XIX, XXI, was the best route.

The structures given to the methylation products (XII), (XIII), (XIX), and (XX) can now be discussed. Corey[30] has shown that bromination of oxosteroids gives axial products when kinetically controlled, Johnson[31] has suggested that this may be true of cationoid substitutions of enols in general, and Robinson has noted other examples.[22] In addition, the order of decreasing specificity of the reduction of the ketones (X), (XII), and (XIII) was probably due to the differences in the sizes of the axial 2"β"-hydrogen, methyl and methoxycarbonyl groups, the increasing size of the 2"β"-substituent causing a progressive decrease in the stability of the (Xa), (XIIa), and (XIIIa) conformations. This evidence all points to the esters (XII) and (XIX), which have been shown to have the same configuration, and are the main products from the methylations of (XI) and (XVIII) respectively, as the *axial* 2"β"-methyl isomers.

It may be thought that if all the configurations assigned in this work are wrong, an equally consistent set of relationships are possible so far as the hydrogenations are concerned which would then conform with Hadler's approach. For this to be possible, the borohydride reduction of the ketone (X) must give the 3"α"-alcohol (XXXI) and then hydrogenation gives the *cis* alcohol (XXXII). But neither product stability (the 3"α"-alcohol (XXXI) has a *pseudo*axial hydroxyl group if the *D*-ring is in the half-chair form) nor steric hindrance favour the formation of (XXXI) unless the *D*-ring is in the half-boat form (as in Xb), in which case product stability must outweigh the increased steric hindrance leading to the 3"β"-alcohol (XXVIII). This in turn requires that the esters (XII) and (XIII), reacting in the same conformation, should be reduced *more* specifically to 3"α"-alcohols of the *cis* series. In fact, the reduction was *less* specific than with (X) and thus supports the main body of evidence that *trans*-octahydrophenanthrenes were obtained.

EXPERIMENTAL

Compounds were frequently purified by passing a concentrated solution in a specified solvent through a short column of alumina (Type A, Messrs. Peter Spence and Co., 0·5–3 g per g of the compound), and evaporating the filtrate and washings before the next operation; for brevity, this will be referred to by the parenthetical phrase "Decolorised in (solvent) with alumina." This simple purification, and a careful choice of reaction conditions, often made wasteful crystallisations and distillations unnecessary before the next reaction. Infra-red spectra were measured for all compounds prepared and were consistent with the structures proposed, but infra-red spectra will only be mentioned specifically in special cases.

6-*Methoxy*-5-*methyl*-1-*tetralone* (III). 6-Methoxy-5-methyltetralin (I) (100 g) was oxidised by the method of Martin and Robinson[11] and the product was isolated by diluting the reaction mixture with brine (5 l.). The tetralone was decolorised in benzene with alumina, and needed no further purification (74 g, 66%), m.p. 110–112°

[30] E. J. Corey *J. Amer. Chem. Soc.* **76**, 175 (1954).
[31] W. S. Johnson *Chem. and Ind.* 167 (1956).

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(Martin and Robinson claim an average yield 70%, m.p. 103–105°, with m.p. 112–113° after purification).

6-Methoxy-2-methoxycarbonyl-2:5-dimethyl-1-tetralone (V). 6-Methoxy-5-methyl-1-tetralone (33·2 g), sodium methoxide (from sodium, 11·5 g) and methyl carbonate (125 c.c., distilled from sodium hydride) were boiled under reflux with stirring in a nitrogen atmosphere (2 hours). Methanol (200 c.c.) and methyl iodide (40 c.c.) were added to the cooled solution, and stirring was continued overnight at room temperature and then at the boiling-point (30 min). The solution was neutralised with 2 N-acetic acid and evaporated, leaving an oil which slowly solidified when shaken with water. The crude ester, in benzene, was decolorised with alumina and then crystallised from light petroleum as large prisms (35 g), m.p. 86–89°. The residues from two runs were recycled and the total yield was raised to 85% (Martin and Robinson obtained an overall yield of 65–69%, m.p. 84–86°, for a three-stage preparation).

6-Methoxy-2:5-dimethyl-1-tetralone (VI). A solution of the ester (V) (40·0 g) in 12 N-hydrochloric acid (90 c.c.), acetic acid (150 c.c.), and water (30 c.c.) was boiled (4 hours) and then left overnight at 0°. The tetralone (VI) separated in laths (29·1 g), m.p. 111–113°; the mother liquors, when diluted with an equal volume of brine, deposited a further quantity of the tetralone (1·4 g), m.p. 110–113° (yield and m.p. after crystallisation from methanol) bringing the total yield to 98% (E. B. J. Smith[32] reported a 75% yield, m.p. 112–113°, after crystallisation).

2-(2′-Cyanoethyl)-6-methoxy-2:5-dimethyl-1-tetralone (VII). Freshly distilled acrylonitrile (5·0 g, 25% excess), in dry *t*-butanol (5 c.c.), was added during 5 min to a stirred suspension of 6-methoxy-2:5-dimethyl-1-tetralone (15·0 g) in dry *t*-butanol (150 c.c.) containing potassium *t*-butoxide (from potassium, 1·5 g) under nitrogen at 30°. The mixture was stirred (4 hours), acidified with 2 N-acetic acid, and evaporated. The oily residue, decolorised in benzene with alumina, crystallised when diluted with methanol and cooled to 0° giving the *nitrile* (VII) (17·4–18·0 g, 92–95%, 2 crops), m.p. 95·5–97·5°, which separated from methanol in prisms, m.p. 96–98° (Found: C, 74·6; H, 7·3; N, 5·5. $C_{16}H_{19}O_2N$ requires C, 74·6; H, 7·4; N, 5·4%).

6-Methoxy-2-(2′-methoxycarbonylethyl)-2:5-dimethyl-1-tetralone (IX). The *nitrile* (VII, previous preparation, 16·25 g) and potassium hydroxide (10 g) in aqueous methanol (1:1, 100 c.c.) were boiled (1 day). The methanol was evaporated under reduced pressure and the cooled residue was added to 4 N-acetic acid (100 c.c.). The precipitated *acid* (VIII) separated from aqueous acetic acid (1:1) in slender needles of the *monohydrate*, m.p. 86–91° (decomp.) (Found: C, 65·0; H, 7·6. $C_{16}H_{20}O_4 \cdot H_2O$ requires C, 65·3; H, 7·5%), which readily lost water at 100°/15 mm and gave the anhydrous acid which solidified in massive prisms, m.p. 92–93° (Found: C, 69·6; H, 7·4. $C_{16}H_{20}O_4$ requires C, 69·5; H, 7·6%). For preparative purposes the crude acid was dried by two evaporations with benzene, and was then boiled (4 hours) with methanol (50 c.c.) and sulphuric acid (1·0 g). From the resulting solution the *methyl ester* (IX) crystallised overnight at 0°, and, after decolorisation in benzene with alumina, separated from methanol in needles (16·9–17·4 g, two crops, 92–95% from the *nitrile*), m.p. 101–102·5° (Found: C, 70·4; H, 7·8. $C_{17}H_{22}O_4$ requires C, 70·3; H, 7·6%).

1:2:3:9:10:11-Hexahydro-7-methoxy-8:11-dimethyl-3-oxophenanthrene (X). (a) 6-Methoxy-2:5-dimethyl-1-tetralone (2·0 g) was added to potassamide (from potassium,

[32] E. B. J. Smith Thesis, Oxford, 1949.

0·8 g) in liquid ammonia (100 c.c.), and the mixture was stirred and evaporated to dryness in a stream of nitrogen during 1 hour. 1-Diethylaminobutan-3-one methiodide (2·90 g), dry ether (25 c.c.), and seven steel ball-bearings were then added and stirring was continued at room temperature (1 hour) and then at the boiling-point (30 min). Ethanol (25 c.c.) was then added and the whole again stirred at the boiling-point (30 min). The mixture was shaken with 2 N-sulphuric acid (20 c.c.) and ether, and when the ethereal layer was evaporated, a small amount of the tetralone (VI) separated from the residue under methanol. After several weeks the residue from the methanol mother liquors partly crystallised, and by washing with pyridine and crystalling twice from methanol, 1:2:3:9:10:11-*hexahydro*-7-*methoxy*-8-11-*dimethyl*-3-*oxophenanthrene* (X) was obtained as pale yellow plates (0·02 g, 1%), m.p. 156–158°, λ_{max}^{MeOH} 248, 330 mμ (ε 13,000, 19,200) (Found: C, 79·5; H, 7·6. $C_{17}H_{20}O_2$ requires C, 79·6; H, 7·8%). The *semicarbazone* precipitated from the pyridine washings when semicarbazide hydrochloride (1·0 g) in water (2 c.c.) was added, and crystallised from acetic acid in pale yellow crystals (0·71 g, 23%), m.p. 262–266° (decomp., rapid heating after immersion at 259°), which turned deep yellow superficially when exposed to air, and was identical with a specimen prepared from the pure ketone (Found: C, 68·7; H, 7·4; N, 13·6. $C_{18}H_{23}O_2N_3$ requires C, 69·0; H, 7·4; N, 13·4%).

(b) 6-Methoxy-2-(2′-methoxycarbonylethyl)-2:5-dimethyl-1-tetralone (IX) (28·7 g), methyl acetate (150 c.c.), sodium methoxide (baked at 150°/15 mm, from sodium, 50 g), ether (50 c.c.), and several glass balls were stirred under nitrogen with slow evaporation (12 hours) of the ether. The resulting pasty solid was baked (2 hours) at 80° and then boiled (18 hours) with formic acid (300 c.c., added slowly). The gummy *product* (isolated with benzene), sodium hydroxide (10 g), water (50 c.c.), and methanol (200 c.c.), were boiled (1 hour), and boiling water (500 c.c.) was added slowly to the mixture. The precipitated solid was collected, washed with hot water (the filtrate and washings contained considerable amounts of the acid (VIII) which was recovered and converted to the methyl ester (IX), 10% after purification), and decolorised in benzene with alumina. The ketone (X) (18·7 g, 82% allowing for recovered ester, 10%), m.p. 154–157°, separated from ethanol in pale yellow needles or, more commonly, plates, m.p. 157–159°, identical with the product from the previous method (Found: C, 79·3; H, 7·8%). The 2:4-*dinitrophenyhydrazone* separated from ethyl acetate in red-brown needles, m.p. 239–241° (decomp.) (Found: C, 63·1; H, 5·7; N, 12·7. $C_{23}H_{24}O_5N_4$ requires C, 63·3; H, 5·6; N, 12·8%). When sodium ethoxide and ethyl acetate were used in the above Claisen condensation, the yield and purity of the product were poorer. When potassium *t*-butoxide and *t*-butyl acetate were used, only ester exchange took place, giving 2-(2′-t-*butoxycarbonylethyl*-6-*methoxy*-2:5-*dimethyl*-1-*tetralone*, which separated from methanol in stout prisms, m.p. 117–119°. (Found: C, 72·1; H, 8·3. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%).

Bromination of 1:2:3:9:10:11-*Hexahydro*-7-*methoxy*-8:11-*dimethyl*-3-*oxophenanthrene* (X). (a) Bromine (0·160 g) in acetic acid (1 c.c.) was added to the ketone (0·256 g) and sodium acetate (0·20 g) in acetic acid (2 c.c.). Crystallisation began after 2–3 min, and aqueous acetic acid (1:1, 4 c.c.) was then added dropwise, giving the 6(?)-*bromo derivative* (0·265 g, 80%), m.p. 159–163°, which separated from methanol in slender needles, m.p. 162·6–164° (Found: C, 60·8; H, 5·7; Br, 23·8. $C_{17}H_{19}O_2Br$ requires C, 60·9; H, 5·7; Br, 23·8%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in scarlet needles, m.p. 209–211° (decomp.) (Found: C, 53·8; H, 4·8;

Br, 15·7. $C_{23}H_{23}O_5N_4Br$ requires C, 53·8; H, 4·5; Br, 15·5%). The 6-bromo derivative was recovered (98%, m.p. 162·5–164°) after boiling (12 hours) with sodium acetate in methanol.

(b) The 6(?)-bromo derivative (0·285 g), bromine (0·18 g), sodium acetate (0·30 g), and acetic acid (3 c.c.) were heated at 50° until colourless (*c.* 30 min), and water (20 c.c.) was then added. The gum which separated crystallised from methanol, giving the 6(?):*x-dibromo derivative* as irregular lumps (0·16 g, 45%), m.p. 148–151° (Found: C, 49·1; N, 4·1; Br, 39·0. $C_{17}H_{18}O_2Br_2$ requires C, 49·3; H, 4·4; Br, 38·4%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in clusters of scarlet needles, m.p. 250–252° (Found: C, 46·8; H, 3·7; N, 9·6; Br, 26·4. $C_{23}H_{22}O_5N_4Br_2$ requires C, 46·5; H, 3·7; N, 9·4; Br, 26·9%). The 6:*x*-dibromo derivative did not react with sodium acetate in boiling methanol.

(c) The ketone (1·02 g), sodium acetate (3·0 g), bromine (2·0 g), and acetic acid (15 c.c.) were heated (2 hours) at 85–90° in a stoppered flask. The addition of aqueous methanol (1:1) precipitated a semi-solid mass which was crystallised twice from benzene-light petroleum, giving a 2ζ:6(?):*x-tribromo derivative* (0·1 g, 5%), m.p. 195–197°, for which satisfactory analytical figures were not obtained. (Found: C, 42·8; H, 3·6; Br, 47·3. $C_{17}H_{17}O_2Br_3$ requires C, 41·4; H, 3·5; Br, 48·3%). Part of the bromine in this ketone was displaced by sodium acetate in boiling methanol, but no crystalline product could be isolated.

1:2:3:9:10:11-*Hexahydro*-17-*methoxy*-8:11-*dimethyl*-2-*oximino*-3-*oxophenanthrene* (XV). *t*-Butyl nitrite (5 c.c.), was added with swirling to the ketone (X) (3·07 g) suspended in *t*-butanol (80 c.c.) containing potassium *t*-butoxide (from potassium, 1·0 g) under nitrogen, and the mixture was left (1 day) at 30°. The resulting orange solution was evaporated at room temperature and the residue, in water, was acidified with carbon dioxide, giving the oximinoketone (XV) (3·00 g, 87%), m.p. *c.* 265° (decomp., very dependent upon the rate of heating), which separated from acetic acid in yellow needles, m.p. *c.* 274° (decomp.) (Found: C, 71·3; H, 6·8. $C_{17}H_{19}O_3N$ requires C, 71·5; H, 6·7%). This compound showed absorption bands with λ_{max}^{MeOH} 260, 360 mμ, but was too sparingly soluble for accurate measurement of the extinction coefficients.

1:2:3:9:10:11"β"-*Hexahydro*-7-*methoxy*-2"α"-*methoxycarbonyl*-8:11"β"-*dimethyl*-3-*oxophenanthrene* (XI). Methyl carbonate was slowly distilled during 4 hours from a boiling mixture of the ketone (X) (1·02 g), sodium methoxide (from sodium, 0·3 g), and methyl carbonate (freshly distilled from sodium hydride, volume maintained at *c.* 10 c.c. while 20–30 c.c. distilled). The cooled residue was shaken with chloroform and saturated aqueous sodium dihydrogen phosphate, and the chloroform layer was evaporated, leaving the *β-oxoester* (XI) (1·22 g, 97%), m.p. 160–171°, which separated from benzene-light petroleum (1:1) in pale yellow needles (1·15 g, 92%), m.p. 170–173°, λ_{max}^{MeOH} 249, 326 mμ (ε 14,300, 21,800) (Found: C, 72·4; H, 7·1. $C_{19}H_{22}O_4$ requires C, 72·6; H, 7·1%). This compound gave a brown coloration after a few seconds with ferric chloride in methanol. The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in red needles, m.p. 219–221° (Found: C, 60·8; H, 5·6. $C_{25}H_{26}O_7N_4$ requires C, 60·7; H, 5·3%).

1:2:3:9:10:11-*Hexahydro*-7-*methoxy*-2-*methoxycarbonyl*-2:8:11-*trimethyl*-3-*oxophenanthrene* (XII *and* XIII). Methyl carbonate and methanol were slowly distilled through a Vigreux column from a boiling mixture of the ketone (X) (5·12 g), sodium

methoxide (from sodium, 0·6 g), and methyl carbonate (b.p. 89°, 60 c.c., freshly distilled from sodium hydride, with two 20-c.c. portions added after 20 min and 1 hour respectively). The rate of distillation was 20 c.c., b.p. 70–87°, in the first 20 min, 20 c.c., b.p. 87–89°, in the next hour, and 20 c.c., b.p. 89°, in the following 3 hours. The resulting yellow slurry was treated with methyl iodide (10 c.c.), boiled (12 hours), cooled, and shaken with water and chloroform. The organic layer was evaporated, leaving a residue (6·4 g, 98%), m.p. 170–180°, which gave no coloration with ferric chloride in methanol, and which on crystallisation from chloroform-methanol (1:5) gave +1:2:3:9:10:11"β"-*hexahydro*-7-*methoxy*-2"α"-*methoxycarbonyl*-2"β":8:11"β"-*trimethyl*-3-*oxophenanthrene* (XII) as pale yellow plates (4·72 g, 72%), m.p. 192·5–194° (unchanged after crystallisation of this compound from methanol), λ_{max}^{MeOH} 249, 330 mμ (ε 12,200, 21,300) (Found: C, 73·1; H, 7·3. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·4%). This *compound*, when treated with bromine (one molecular equivalent) and sodium acetate in acetic acid at room temperature gave a 6-*bromo derivative*, which separated from ethanol in prismatic needles, m.p. 190–192° (Found: C, 59·0; H, 5·8; Br, 19·6. $C_{20}H_{23}O_4Br$ requires C, 59·0; H, 5·7; Br, 19·6%). The residue from the chloroform mother liquors was crystallised thrice from benzene-light petroleum, giving 1:2:3:9:10:11"β"-*hexahydro*-7-*methoxy*-2"β"-*methoxycarbonyl*-2"α":8:11-"β"-*trimethyl*-3-*oxophenanthrene* (XIII) as pale yellow needles (0·80 g, 12%), m.p. 161–164°, λ_{max}^{MeOH} 248,330 mμ (ε 13,200, 23,700) (Found: C, 73·1; H, 7·4. $C_{20}H_{24}O_4$ requires C, 73·1; H, 7·4%).

1:2:3:9:10:11"β"-*Hexahydro*-7-*methoxy*-2"α":8:11"β"-*trimethyl*-3-*oxophenanthrene* (XIV). The β-oxoester (XII) (0·72 g), sodium hydroxide (1·0 g), methanol (25 c.c.), and water (5 c.c.) were boiled (1 day). The solution was concentrated to *c.* 15 c.c. and treated, at the boil, with water (15 c.c.) added dropwise, giving the 2"α"-*methyl ketone* (XIV) (0·56 g, 95%), m.p. 159–162°, which separated from methanol in prisms, m.p. 160·5–162·5°, λ_{max}^{MeOH} 248, 328 mμ (ε 13,800, 21,500) (Found: C, 79·7; H, 8·1. $C_{18}H_{22}O_2$ requires C, 80·0; H, 8·2%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in scarlet needles, m.p. 222–224° (Found: C, 63·7; H, 5·8. $C_{24}H_{26}O_5N_4$ requires C, 64·0; H, 5·8%). When the hydrolysis was stopped after 12 hours boiling, *sodium* 1:2:3:9:10:11"β"-*hexahydro*-7-*methoxy*-2"β":8:11"β"-*trimethyl*-3-*oxophenanthrene*-2"α"-*carboxylate trihydrate* (0·08 g, 12%) crystallised from the aqueous filtrate and was recrystallised from moist acetone in needles, m.p. 190–200° (decomp.) (Found: C, 58·6; H, 7·1. $C_{19}H_{21}O_4Na{\cdot}3H_2O$ requires C, 58·5; H, 7·0%). The ketone (XIV) was obtained from the above sodium salt by warming with 2 N-acetic acid, and by boiling (10 hours) with 2 N-sodium hydroxide, and from the ester (XIII) (previous preparation) by alkaline hydrolysis.

1:2:3:4:9:10:11"β":12"α"-*Octahydro*-3"β"-*hydroxy*-7-*methoxy*:8:11"β"-*dimethylphenanthrene* (XXIV). (a) Lithium (0·2 g) was added during 20 min to the ketone (X) (0·51 g) in dry dioxan (10 c.c.), ether (10 c.c.), ethanol (2 c.c.), and liquid ammonia (150 c.c.). When the blue colour had faded, ammonium chloride (2 g) was added and the ammonia was evaporated. The residue was washed with water and then crystallised twice from methanol, giving the *alcohol* (XXIV) (0·21 g, 40%) as slender needles, m.p. 154–157° (Found: C, 78·7; H, 9·2. $C_{17}H_{24}O_2$ requires C, 78·4; H, 9·3%).

(b) The ketone (X) (0·51 g) in methanol (40 c.c.) was reduced with hydrogen (uptake 3·99 atoms per molecule during 4–8 hours) in the presence of palladium on

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strontium carbonate (5%, 0·25 g) at atmospheric pressure and room temperature. The resulting solution was filtered through sodium sulphate and evaporated, leaving a residue (0·51 g, no colour with formic acid) which crystallised from methanol, giving the *alcohol* (XXIV) (0·30 g, 60%) as needles, m.p. 154–157°, undepressed by the specimen prepared above.

(c) Potassium borohydride (0·3 g) in water (1·5 g) was added to the ketone (X) (1·00 g) suspended in methanol (20 c.c.), the mixture was left overnight at 30° and then treated with water (10 c.c.) added dropwise. After 2 hours the precipitated solid was collected and washed with water, giving 1:2:3:9:10:11"*β*"-*hexahydro*-3"*β*"-*hydroxy*-7-*methoxy*-8:11"*β*"-*dimethyphenanthrene* (XXVIII) (0·83–0·87 g, 82–86%), m.p. 157–160°, which separated from methanol in irregular plates, m.p. 159–161°, λ_{max}^{MeOH} 267 mμ (ε 15,900). The melting-point of this alcohol was depressed only to 151–155° when this unsaturated alcohol was mixed with an equal weight of the saturated alcohol (XXIV), m.p. 154–157°. The alcohol (XXVIII) (0·80 g) in ethanol (20 c.c.) was reduced with hydrogen (uptake 1·6–1·7 atoms per molecule in 1–2 hours) in the presence of palladium on strontium carbonate (5%, 0·8 g) at atmospheric pressure and room temperature. The resulting solution was filtered through sodium sulphate and evaporated, leaving the alcohol (XXIV) (0·80 g, 99%) m.p. 154–157°, undepressed by the specimens prepared above. The *acetate*, prepared with acetic anhydride in pyridine at room temperature, separated from methanol in needles, m.p. 93–94° (Found: C, 75·5; H, 8·8. $C_{19}H_{28}O_3$ requires C, 75·5; H, 8·7%).

1:2:3:4:9:10:11:12-*Octahydro*-7-*methoxy*-8:11-*dimethyl*-3-*oxophenanthrene* (two isomers, XVII and XXII). (a) The ketone (X) (0·51 g) in toluene (5 c.c.) and ether (15 c.c.) was added to lithium (0·040 g) in liquid ammonia (50 c.c.) and the mixture was stirred (4 hours). After the addition of ammonium chloride (1 g) and evaporation, the product (0·50 g) was isolated with ether and dissolved in boiling methanol (5 c.c.) containing 2 N-hydrochloric acid (1 drop), from which 1:2:3:4:9:10:11"*β*":12"α"-*octahydro*-3:3:7-*trimethoxy*-8:11"*β*"-*dimethylphenanthrene* (the dimethyl ketal of the *trans* ketone XVII) separated in prisms (0·30 g, 50%), m.p. 115–117° (Found: C, 74·9; H, 9·3. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%). The dimethyl ketal (0·195 g)-toluene-*p*-sulphonic acid (0·01 g) and acetone (4 c.c.) were boiled (15 min). When the resulting solution was evaporated to about 2 c.c. and diluted with water (4 c.c.), the trans *ketone* (XVII) separated in stout needles (0·14 g, 85%), m.p. 140–141° (Found: C, 79·0; H, 8·9. $C_{17}H_{22}O_2$ requires C, 79·0; H, 8·6%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in yellow prisms, m.p. 221–223° (Found: C, 63·5; H, 5·9. $C_{23}H_{26}O_5N_4$ requires C, 63·2; H, 6·0%). The crude product from the above reduction, after slow crystallisation from methanol, could be separated by hand-picking, giving the *trans* ketone (XVII) as irregular lumps, m.p. 137–140° (undepressed by a pure specimen), and the *cis* ketone (XXII) which separated from methanol after three crystallisations as plates, m.p. 99–101° (Found: C, 79·2; H, 8·4%). Neither isomer gave any coloration in formic acid.

(b) 1:2:3:4:9:10:11"*β*":12"α"-Octahydro-3"*β*"-hydroxy-7-methoxy-8:11"*β*"-dimethylphenanthrene (XXIV) (0·5 g) in pyridine (5 c.c.) was added to chromium trioxide (0·5 g) in pyridine (5 c.c.). After 12 hours ether and water were added and the ethereal layer was evaporated on the water-bath. The residue (mainly pyridine) was diluted with water (10 c.c.) and the product (0·40 g, 80%, pale yellow coloration with formic acid), m.p. 138–140°, was crystallised from methanol, giving the *trans* ketone

(XVII), m.p. 140–141°, undepressed by the specimen prepared above. When the aqueous pyridine mother liquors were diluted again with water, a precipitate formed which gave a strong formic acid colorisation, qualitatively similar to that given by the ketone (X), and which formed a red-brown precipitate with 2:4-dinitrophenylhydrazine but too little material was available for purification.

1:2:3:4:9:10:11"β":12"α"-*Octahydro*-7-*methoxy*-2"α"-*methoxycarbonyl*-8:11"β"-*dimethyl*-3-*oxophenanthrene* (XVIII). The *trans* ketone (XVII) (0·50 g), sodium methoxide (from sodium, 0·2 g), and methyl carbonate (15 c.c.) were boiled (4 hours). After cooling, aqueous sodium dihydrogen phosphate and ether were added and the organic layer was evaporated, leaving the β-oxoester (XVIII) (0·60 g, 98%), m.p. 147–150°, which separated from methanol in needles, m.p. 150–151° (Found: C, 72·0; H, 7·9. $C_{19}H_{24}O_4$ requires C, 72·1; H, 7·7%). This β-oxoester gave a violet colour with methanolic ferric chloride.

1:2:3:4:9:10:11"β":12"α"-*Octahydro*-3"β"-*hydroxy*-7-*methoxy*-2"α"-*methoxycarbonyl*-2"β":8:11"β"-*trimethylphenanthrene* (XXVI). The β-oxoester (XII) (4·73 g) in tetrahydrofuran (80 c.c.) and methanol (100 c.c.) at 50° was treated with potassium borohydride (3·0 g) in water (10 c.c.) and the mixture was left at 50° (30 min) and at room temperature (12 hours). The reduction was complete when an acidified sample, boiled (1 hour) with an excess of alkali, formed no 2:4-dinitrophenylhydrazone after reacidification. The solution was acidified with acetic acid until no more hydrogen was evolved, evaporated to *c.* 30 c.c., and diluted slowly with boiling water (40 c.c.), and the resulting slurry was left at 100° for 10 min. 1:2:3:9:10:11"β"-*Hexahydro*-3"β"-*hydroxy*-7-*methoxy*-2"α"-*methoxycarbonyl*-2"β":8:11"β"-*trimethylphenanthrene* (XXIX) was collected (4·25 g, 90%), m.p. 180–182° (with presoftening), and crystallised from chloroform-methanol (1:3) in thick plates, m.p. 182–184°, λ_{max}^{MeOH} 265 mμ (ε 10,500) (Found: C, 72·5; H, 8·2. $C_{20}H_{28}O_4$ requires C, 72·7; H, 7·9%). In one experiment the yield of crude product was nearly theoretical but the purity was much lower and recrystallisation was necessary before the next reaction. The unsaturated hydroxyester (2·60 g) suspended in ethanol (100 c.c.) was reduced with hydrogen (the uptake could not be measured accurately above room temperature in the apparatus used) in the presence of palladium on strontium carbonate (5%, 2·0 g) during 3 hours at atmospheric pressure and at 50–60°. The mixture was diluted with hot chloroform (100 c.c.) to dissolve the product, and filtered through sodium sulphate, evaporated to *c.* 20 c.c., and left overnight at 0°. The *hydroxyester* (XXVI) (2·20 g, 85%), m.p. 200–202° (with softening at 196°) was collected and then crystallised from chloroform-methanol (1:4) in prisms, m.p. 200–202° (Found: C, 72·2; H, 8·5. $C_{20}H_{28}O_4$ requires C, 72·3; H, 8·5%).

1:2:3:4:9:10:11"β":12"α"-*Octahydro*-7-*methoxy*-2"α"-*methoxy*-*carbonyl*-2-"β":8:11"β"-*trimethyl*-3-*oxophenanthrene* (XIX). (a) The β-oxoester (XVIII) (0·30 g) in methanol (10 c.c.) was treated successively with sodium methoxide (from sodium, 0·3 g) and methyl iodide (2·5 c.c.) and the mixture was left (12 hours) at room temperature. The resulting solution was shaken with ether and water (containing acetic acid, 3 drops) and the ethereal layer was evaporated under reduced pressure. The residue (0·31 g, no coloration with methanolic ferric chloride), m.p. 130–158°, was crystallised from chloroform-methanol (1:4), giving the 2"β"-methyl derivative (XIX) (0·17 g, 55%) m.p. 170–174, which then separated from methanol in plates, m.p. 173–175° (Found: C, 72·6; H, 8·0. $C_{20}H_{26}O_4$ requires C, 72·7; H, 7·9%). From the

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mother liquors was isolated a small quantity of a substance separating from methanol in prisms, m.p. 168–169·5°, which was almost certainly the 2"α"-methyl ester (XX), although satisfactory analytical figures were not obtained. (Found: C, 71·1; H, 7·6%). (b) The hydroxyester (XXVI) (2·65 g) in pyridine (30 c.c.) at *c.* 30° was added to chromium trioxide (2·5 g) in pyridine (25 c.c.), and the mixture was left (36 hours) at 20°. Ether (40 c.c.) and chloroform (20 c.c.), followed after 5 min by water (50 c.c.), were added and the mixture was filtered. The organic layer was washed with water and evaporated to dryness (100°/15 mm). The residue (2·47 g, 94%), m.p. 169–171·5° (with softening at 162°), crystallised from chloroform-methanol (1:3), giving the β-oxoester (XIX), m.p. 172–174°, undepressed by the specimen prepared above. The crude product gave a weak coloration with formic acid, which was presumably due to a trace of the unsaturated β-ketoester (XII). When the oxidation was stopped after only 12 hours, some of the hydroxyester (XXVI) remained unchanged and could not be completely removed by crystallisation, but a pure product was obtained after treatment with succinic anhydride in pyridine (12 hours at room temperature) and dilute alkali.

1:2:3:4:9:10:11"β":12("α" *and* "β")-*Octahydro*-7-*methoxy*-2"β":8:11"β"-*trimethyl* 3-*oxophenanthrene* (two isomers, XXI and XXIII). (a) 1:2:3:9:10:11"β"-Hexahydro-7-methoxy-2"α":8:11"β"-trimethyl-3-oxophenanthrene (XIV) (0·54 g) in toluene (5 c.c.) and ether (10 c.c.) was added to lithium (0·04 g) in liquid ammonia (100 c.c.). After 2 hours lithium (0·02 g), and after a further 4 hours ammonium chloride (1 g), were added, and the solvents were evaporated. The product, isolated with ether, crystallised from methanol as prisms (0·51 g, 94%), m.p. 109–115°, unchanged by further crystallisation from methanol, and the mixture of ketones were converted into ethylene ketals. Benzene (*c.* 400 c.c.) was slowly distilled during 3 hours from a stirred mixture of the mixed ketones (0·50 g), ethylene glycol (2 c.c.), toluene-*p*-sulphonic acid (0·02 g), and dry benzene (volume maintained at *c.* 50 c.c.). The cooled solution was washed with N-sodium hydrogen carbonate (20 c.c.), dried and evaporated. The residue, under ether-methanol, crystallised after several days, giving the *ethylene ketal* of the *trans* ketone (XXI), which separated from methanol containing pyridine (1 drop) as prisms (0·31 g, 50%), m.p. 100–102° (Found: C, 75·9; H, 8·9. $C_{20}H_{28}O_3$ requires C, 75·9; H, 8·9%). This ketal (0·20 g), acetone (3 c.c.), and 10-N hydrochloric acid (0·05 c.c.) were boiled (15 min) and then treated with water (3 c.c.) added dropwise, giving the trans *ketone* (XXI) (0·155 g, 90%), m.p. 120–125°, which separated from methanol in granules (0·14 g, 80%), m.p. 126–128° (Found: C, 79·4; H, 8·8. $C_{18}H_{24}O_2$ requires C, 79·3; H, 8·8%). The 2:4-*dinitrophenylhydrazone* separated from ethyl acetate in orange needles, m.p. 198–202° (Found: C, 63·6; H, 6·3. $C_{24}H_{28}O_5N_4$ requires C, 63·7; H, 6·2%). The residues from the crystallisation of the ketal were hydrolysed in the same way as the crystalline ketal and the product slowly separated as prisms when seeded with the original mixture of ketones. After trituration with methanol, the prisms, m.p. 95–105°, dissolved readily in boiling methanol and sparingly soluble plates immediately separated, and after two more crystallisations from methanol the 2"ζ"-*methyl* cis *ketone* (XXIII) was obtained in irregular plates (0·03 g, 10%), m.p. 137–140° (Found: C, 78·8; H, 8·7. $C_{18}H_{24}O_2$ requires C, 79·3; H, 8·8%). This specimen showed a weak infra-red absorption band at 1650 cm^{-1} which was presumably due to a small amount of the unreduced ketone (XIV).

(b) Potassium borohydride (0·5 g) in water (3 c.c.) was added to the ketone (XIV)

(0·50 g) in tetrahydrofuran (10 c.c.) and methanol (5 c.c.). The solution was left (12 hours) at 30°, concentrated to *c.* 5 c.c. and then left (4 hours) at 0°. The product (0·40 g), m.p. 135–145°, was collected and crystallised twice from methanol, giving long needles (0·15 g, 30%), m.p. 160–163°, which gave an orange coloration with formic acid but by analysis appeared to be mainly a saturated rather than allylic alcohol. This product (0·12 g), in methanol (5 c.c.), was reduced with hydrogen (uptake 0·26 atoms per molecule) in the presence of palladium on strontium carbonate (5%, 0·10 g) at atmospheric pressure and room temperature. The solution was filtered through sodium sulphate and evaporated. The residue (0·12 g) crystallised from chloroform-methanol (1:4), giving the 2"α"-*methyl*-3"β"-*alcohol* (XXV) (0·11 g, 22%), m.p. 162–163° (Found: C, 78·7; H, 9·6. $C_{15}H_{28}O_2$ requires C, 78·8; H, 9·5%). This alcohol was oxidised by the method used for the alcohol (XXIV), and resulting ketone (XXI) (70%), m.p. 126–128°, was identical with the specimen prepared above (in (a)).

(c) The β-oxoester (XIX) (1·0 g), acetic acid (12·5 c.c.), 10-N hydrochloric acid (5 c.c.), and water (2·5 c.c.) were boiled (16 hours) and then water (10 c.c.) was added dropwise. The brown product, decolorised in benzene with alumina, crystallised from methanol, giving the ketone (XXI) (0·70 g, 85%), m.p. 126–128°, which separated from methanol after two more crystallisations as short prisms, m.p. 126–128°, identical with the specimens prepared before. When the hydrolysis was carried out with alkali, using conditions similar to those suitable for the ester (XII), a colourless and more easily purified product was obtained in 90–95% yield.

The author thanks his supervisor, Sir Robert Robinson, for constant help and discussion and for making available a considerable amount of the tetralone (V); the Department of Scientific and Industrial Research and the Rockefeller Foundation for maintenance grants; and Mr. F. Hastings, under the supervision of Dr. Strauss, for measurements of spectra.

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Tetrahedron, 1957, Vol. 1, pp. 67–74. Pergamon Press Ltd., London.

ÜBER DEN MECHANISMUS DER SYNTHESE METALLORGANISCHER VERBINDUNGEN MITTELS DER DIAZONIUM-DOPPELSALZE

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(*Received* 10 *January* 1957)

Zusammenfassung—Es wird die Kinetik der Zersetzung von Doppelsalzen des Typs p-$XC_6H_4SbCl_4$·p-$YC_6H_4N_2Cl$ durch Eisenpulver in aceton untersucht. Die Reaktion verläuft unter Bildung von Diaryltrichlorstibinen $XC_6H_4(YC_6H_4)SbCl_2$. Der Die Substituenten X erhöhen die Reaktionsgeschwindigkeit in der Reihenfolge: $O_2N < Cl < H < CH_3 < C_2H_5O$. Die Substituenten Y erhöhen die Reaktionsgeschwindigkeit in der Folge: $C_2H_5O < CH_3 < H$. Die Beständigkeit der Doppelsalze p-$XC_6H_4SbCl_4$·p-$YC_6H_4N_2Cl$ in Abhängigkeit vom Charakter der Substituenten X und Y wird untersucht. Die Salze dieses Types werden leicht unter Bildung von $XC_6H_4(YC_6H_4)SbCl_2$ zerlegt. Elektronegative Substituenten X und elektropositive Substituenten Y erhöhen die Beständigkeit der Salze. Elektropositive X und elektronegative Y setzen deren Beständigkeit herab. Es wird die Vermutung ausgesprochen, dass die Umsetzung der Diazoniumdoppelsalze mit Metallpuiver die zur Bildung von metallorganischen Verbindungen führt (Nesmejanow-Reaktion), einen heterolytischen Prozess darstellt. Der Zusammenhang zwischen der Reaktion von Nesmejanow und der von Waters wird betrachtet.

Abstract—The kinetics of decomposition of double salts p-$XC_6H_4SbCl_4$·p-$YC_6H_4N_2Cl$ by powdered iron in acetone was studied. The reaction proceeds with the formation of diaryltrichlorostibine $XC_6H_4(YC_6H_4)SbCl_2$. The substitutes X increase the rate of reactions in order : $O_2 < Cl < H < CH_3 < C_2H_5O$. The substitutes Y increase the rate of reactions in order: $C_2H_5O < CH_3 < H$. The relationship between the stability of the double salts p-$XC_6H_4SbCl_4$·$YC_6H_4N_2Cl$ and the character of substitutes X and Y was studied. The salts of this type decomposed readily to form XC_6H_4·$(YC_6H_4)SbCl_2$. The electronegative substitutes X and electropositive substitutes Y increase the stability of the salts. The electropositive X and electronegative Y decrease the stability of the salts. The mechanisms of the reactions are discussed. The assumption has been made that the decompositon of double diazonium salts by metal powders, leading to the formation of organometallic compounds (the Nesmeyanow reaction) is heterolythic in character. The relationship between the Nesmeyanow reaction and Waters reaction has been discussed.

IM Jahre 1929 stellte A. N. Nesmejanow[1] fest, dass bei der Einwirkung von Metallpulvern auf Diazonium-Doppelsalze metallorganische Verbindungen entstehen:

$$ArN_2X{\cdot}MeX_n \xrightarrow{Me'} Ar_nMeX_{p-n} \quad \text{oder} \quad Ar_nMe'X_{p-n}$$

(p und q sind die Wertigkeiten der Metalle Me und Me′)

[1] A. N. Nesmejanow *Journal der Russischen Physikalisch-Chemischen Gesellschaft* **61**, 1393 (1929); *Ber.* **62**, 1010 (1929).

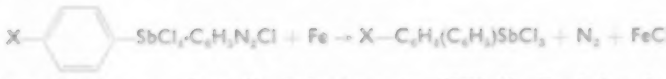
Die Nesmejanow-Reaktion wurde später zu einer Methode der Synthese metallorganischer Verbindungen des Quecksilbers,[2-6] Zinns,[7,8] Bleis,[9,10] Arsens,[11] Antimons,[12-20] Wismuts,[21] und Talliums[22] entwickelt.

Es wird heute allgemein angenommen, dass die Nesmejanow-Reaktion ein homolytischer Process ist, der durch das Stadium neutraler Radikale verläuft.

Diese Vorstellungen, hauptsächtlich durch die Untersuchungen von W. A. Waters[23] geschaffen, stützen sich auf die Tatasche, dass bei der Nesmejanow-Reaktion solche Nebenprodukte beobachtet wurden, die nur durch Reaktionen neutraler Arylradikale und Chloratome entstehen können (Kohlenwasserstoffe ArH, Lösungsmittel-Chlorierungsprodukte). Die beobachteten Nebenprodukte können jedoch das Resultat homolytischer Nebenreaktionen sein, während die Hauptreaktion, die zur Bildung der metallorganischen Verbindungen führt, auch heterolytisch verlaufen könnte.

Es gelang uns festzustellen,[24] dass die Diazoniumdoppelsalze unter den Bedingungen der Nesmejanow-Reaktion zur Dissoziation fähig sind, wobei freies Aryldiazonium entsteht. Die Zersetzung des Aryldiazoniumchlorides durch ein Metallpulver (oder die thermische Zersetzung), führt zu der Bildung von freien Radikalen, die mit dem Lösungsmittel reagieren. Das ist aber eine Nebenreaktion, die wahrscheinlich in keiner direkten Beziehung zu der Hauptreaktion steht d.h. der Reaktion zwischen dem Diazoniumdoppelsalz und dem Metall, die zur Entstehung der metallorganischen Verbindung führt.

Wir untersuchten die Abhängigkeit der Reaktionsgeschwindigkeit gemäss folgender Gleichung vom Charakter des Substituenten "X".[25]



Es stellte sich heraus, dass die Substituenten "X" die Reaktion in dem Masse

[2] A. N. Nesmejanow u. E. I. Kan *J. Russ. Phys. Chem. Ges.* **61**, 1407 (1929); *Ber.* **62**, 1018 (1929).
[3] A. N. Nesmejanow u. I. T. Eskin *Nachr. Acad. Wiss. UdSSR, Abt. Chem. Wiss.* 116 (1942).
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[7] A. N. Nesmejanow, K. A. Kotscheschkow, u. W. A. Klimowa *Ber.* **68**, 1877 (1935); K. A. Kotscheschkow, A. N. Nesmejanow, u. W. A. Klimowa *Z. Allg. Chem.* **6**, 167 (1936).
[8] A. N. Nesmejanow u. L. G. Makarowa *Ber. Acad. Wiss. UdSSR* **87**, 421 (1952).
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[10] A. N. Nesmejanow, K. A. Kotscheschkow, u. M. M. Nad *Nachr. Acad. Wiss. UdSSR, Abt. Chem. Wiss.* 522 (1945).
[11] O. A. Reutow u. J. G. Bundel *Nachr. Moskauer Staatl. Univ.* **N8**, 85 (1955).
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[14] O. A. Reutow u. A. Markowskaja *Ber. Acad. Wiss. UdSSR* **98**, 979 (1954).
[15] O. A. Reutow, A. Markowskaja u. A. N. Lowzowa *Ber. Acad. Wiss. UdSSR* **99**, 269 (1954).
[16] A. N. Nesmejanow, O. A. Reutow u. P. G. Knoll *Nachr. Acad. Wiss. UdSSR, Abt. Chem. Wiss.* 410 (1954).
[17] O. A. Reutow *Ber. Acad. Wiss. UdSSR* **87**, 991 (1952).
[18] O. A. Reutow u. W. W. Kondratjewa *Z. Allg. Chem.* **24**, 1259 (1954).
[19] A. N. Nesmejanow, O. A. Reutow u. O. A. Ptizina *Ber. Acad. Wiss. UdSSR* **91**, 1341 (1953).
[20] O. A. Reutow u. A. Markowskaja *Ber. Acad. Wiss. UdSSR* **99**, 543 (1954).
[21] T. K. Kosminskaja, M. M. Nad, u. K. A. Kotscheschkow *Z. Allg. Chem.* **16**, 891 (1946).
[22] A. N. Nesmejanow u. L. G. Makarowa *Ber. Acad. Wiss. UdSSR* **87**, 417 (1952).
[23] W. A. Waters *The Chemistry of Free Radicals* Oxford 1946 (Moskau, Verlag für ausländ. Lit., 1948, S. 178).
[24] A. Markowskaja *Diss. Moskau* (1955).
[25] O. A. Reutow, A. Markowskaja, u. P. E. Mardaleischwilli *Ber. Acad. Wiss. UdSSR* **104**, 253 (1955).

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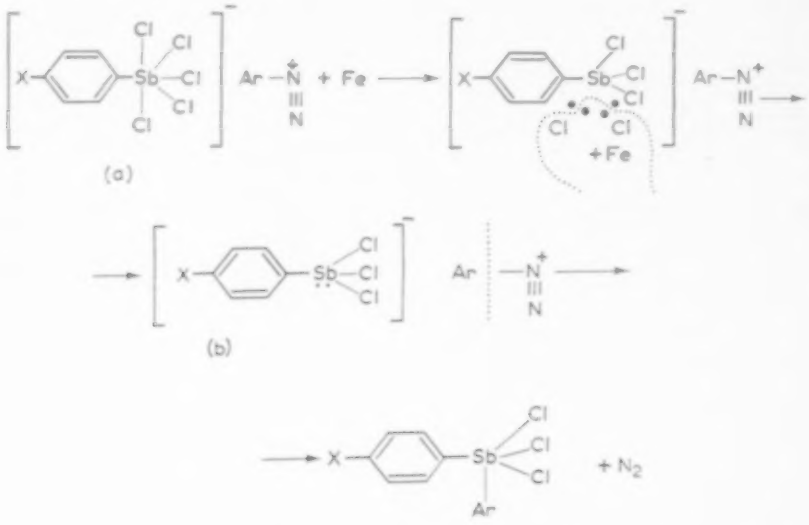
beschleunigen, in welchem ihre Elektronabstossenden Eigenschaften steigen:

$$O_2N < Cl < H < CH_3 < C_2H_5O$$

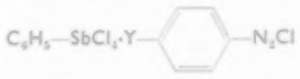
Da die Elektronen-Dichte bei Radikalreaktionen nicht der bestimmende Faktor ist (vergleiche z.B.[26]), so ist eine solche einfache Abhängigkeit der Reaktionsgeschwindigkeit von den elektronegativen Eigenschaften der Substituenten unverständlich, wenn die Reaktion als eine homolytische aufgefasst wird.

Die beobachtete Abhängigkeit kann aber bei der Annahme eines heterolytischen Charakters der Zersetzung von Diazoniumdoppelsalzen durch das Eisenpulver ihre Erklärung erhalten, z.B. nach folgendem Schema:

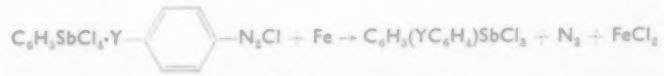


Dabei ist es ganz natürlich, dass die Zersetzung des intermediär gebildeten Doppelsalzes (B) (—die Addition des Aryl-Kations zum freien Elektronenpaar des Antimons) durch die Substituenten I Ordnung beschleunigt und durch die Substituenten II Ordnung verzögert wird.

Die Abhängigkeit der Zersetzungsgeschwindigkeit der Doppelsalze



vom Charakter des Substituenten Y



ist auch durch die Annahme des heterolytischen Charakters der untersuchten Reaktion erklärbar: mit dem Ansteigen der elektronenabstossenden Eigenschaften der Substituenten fällt die Reaktionsgeschwindigkeit:

$$H > CH_3 > C_2H_5O$$

[26] D. Hey *Quarterly Reviews* **8**, 308 (1954).

In dem Falle, wenn Y-Substituenten II Ordnung sind (NO_2, $COOC_2H_5$), ist das Doppelsalz in der Acetonlösung merklich dissoziiert und bei der Einwirkung von Eisenpulver verlaufen zwei Reaktionen: die Zersetzung des Doppelsalzes und die Zersetzung des freien Aryldiazoniums.

Die im obene Schema als Zwischenprodukte angegebenen Doppelsalze (B)—$ArSbCl_2 \cdot ArN_2Cl$ wurden von uns nach folgender Reaktion hergestellt

$$ArSbCl_2 + Ar'N_2Cl \cdot FeCl_3 \rightarrow ArSbCl_2 \cdot Ar'N_2Cl + FeCl_3$$

und einer systematischen Untersuchung unterworfen:[27]

Dabei konnten wir feststellen, dass die Beständigkeit dieser Salze verschieden ist und vom Charakter von Ar und Ar′ abhängig ist. Folgende Tafel enthält die von uns untersuchten Salze, wobei das Zeichen ⊕ bedeutet, dass das Salz dargestellt wurde, das Zeichen — bedeutet dass das Salz nicht existenzfähig ist.

Ausgangsdoppelsalz $Ar'N_2Cl \cdot FeCl_3$	Ausgangsaryldichlorstibin $ArSbCl_2$			
	p-$O_2NC_6H_4SbCl_2$	p-$H_2NO_2SC_6H_4SbCl_2$	$C_6H_5SbCl_2$	p-$CH_3C_6H_4SbCl_2$
p-$O_2NC_6H_4N_2Cl \cdot FeCl_3$	—	—	—	—
m-$O_2NC_6H_4N_2Cl \cdot FeCl_3$	—	—	—	—
p-$C_2H_5OCOC_6H_4N_2Cl \cdot FeCl_3$	—	—	—	—
p-$CH_3COC_6H_4N_2Cl \cdot FeCl_3$	⊕	—	—	—
$C_6H_5N_2Cl \cdot FeCl_3$	⊕	⊕	⊕	—
p-$CH_3C_6H_4N_2Cl \cdot FeCl_3$	⊕		⊕	⊕
p-$CH_3OC_6H_4N_2Cl \cdot FeCl_3$	⊕		⊕	⊕
p-$C_2H_5OC_6H_4N_2Cl \cdot FeCl_3$		⊕	⊕	
p-$(CH_3)_2NC_6H_4N_2Cl \cdot FeCl_3$	⊕	⊕	⊕	⊕

Man sieht, dass Substituenten I Ordnung im Radikal der antimonorganischen Verbindung die Beständigkeit der Doppelsalze herabsetzen, die gleichen Substituenten im Diazoniumradikal erhöhen sie. Die Substituenten II Ordnung im Radikal der antimonorganischen Komponente dagegen erhöhen die Beständigkeit, während dieselben Substituenten im Diazoniumradikal sie herabsetzen. Viele Salze,—besonders solche, die einen Substituenten II Ordnung im Diazoniumradikal und einen Substituenten I Ordnung im Radikal der antimonorganischen Komponente enthalten,—sind unbeständig und alle Versuche sie herzustellen schlugen fehl—es trat eine sofortige Zersetzung unter Bildung des Diarylantimontrichlorids ein.

Diese Erscheinung ist unerklärbar, wenn man auf dem heute üblichen Standpunkt über den Radikalcharakter der Zersetzung der Diazoniumdoppelsalze steht:

$$ArSbCl_2 \cdot Ar' \; \vdots\!\!\cdot\!\!\vdots \; N_2 \; \vdots\!\!\cdot\!\!\vdots \; Cl \rightarrow ArAr'SbCl_3 + N_2$$

Bei der Annahme des heterolytischen Verlaufs der Reaktion

$$[ArSbCl_2]^- Ar' \; \vdots \; N^+ \rightarrow ArAr'SbCl_3 + N_2$$

kann die Abhängigkeit der Beständigkeit von Aryldichlorstibindiazoniumdoppelsalzen von dem Charakter von Ar und Ar′ ihre Erklärung erhalten.

[27] O. A. Reutow u. O. A. Ptizina *Ber. Acad. Wiss. UdSSR* **102**, 291 (1955).

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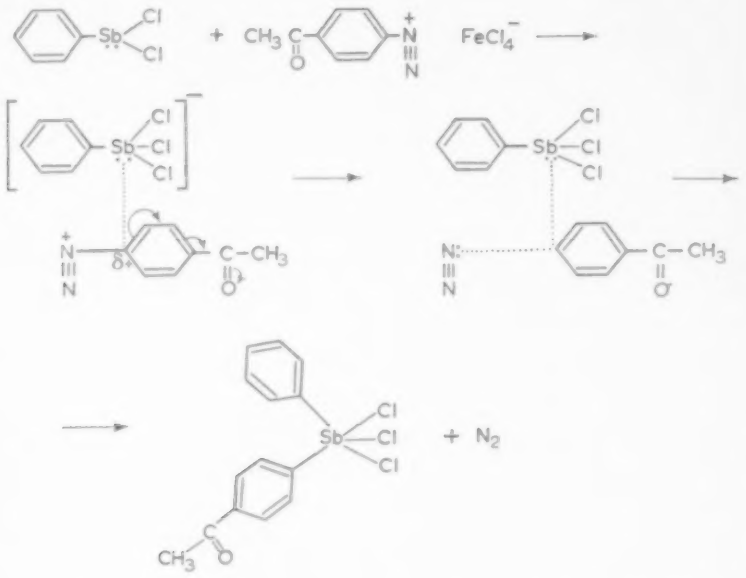
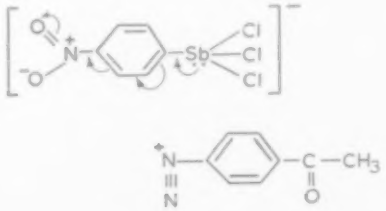
Die Unbeständigkeit von Diazoniumdoppelsalzen mit einem Substituenten II Ordnung im Diazoniumradikal ist durch die Wechselwirkung zwischen dem Anion der antimonorganischen Verbindung und dem Aryldiazoniumkation bedingt. Diese Wechselwirkung kommt dadurch zustande, dass das Antimonatom ein freies Elektronenpaar und das mit dem Stickstoff verbundene Ringkohlenstoffatom- eine positive Ladung aufweisen, die durch die elektronenabziehende Wirkung des Substituenten II Ordnung bedingt ist.



Wenn in die Ortho- oder Para-Stellung des Phenyldichlorstibinradikals ein Substituent II Ordnung eingeführt wird, so verschiebt sich das freie Elektronenpaar des Antimon-Atoms zum Benzolring hin.

Dadurch wird die Wechselwirkung des Antimonatoms mit dem Kohlenstoffatom des Diazonium-Radikals geschwächt, was zum Anwachsen der Beständigkeit des Doppelsalzes führt. Das ist wahrscheinlich die Erklärung dafür, dass das *p*-Nitrophenyldichlorstibin auch mit solchen Aryldiazohalogeniden beständige Salze gibt, die einen Substituenten II Ordnung enthalten (Acetyl).



Die angeführten Tatsachen zwingen uns, die Vorstellungen von dem homolytischen Charakter der Synthese metallorganischer Verbindungen mittels der Diazonium

Doppelsalze (—und in erster Linie der Nesmejanow-Reaktion) zu revidieren und die Meinung auszusprechen, dass die Reaktion heterolytisch verläuft.

Betrachten wir nun mehr kurz die Frage des Zusammenhanges der Nesmejanow-Reaktion mit der Waters-Reaktion.

Nach Waters[23] bildet sich im Verlauf der Nesmejanow-Reaktion bei der Reduktion des Doppelsalzes freies Metall, das weiter mit dem Aryldiazoniumhalogenid homolytisch reagiert, z.B. nach folgenden Schema:

$$ArN_2Cl \cdot HgCl_2 + 2Cu \longrightarrow ArN_2Cl + Hg + Cu_2Cl_2$$

$$Ar\cdot\ \ddot{N}_2\ddot{Cl} + \cdot Hg\cdot \longrightarrow ArHgCl + N_2$$

Das steht aber im Wiederspruch zu einer Anzahl von Tatsachen:

1. Bei der Zersetzung des Diazoniumdoppelsalzes des Sublimats durch Silberpulver bildet sich wie in Falle des Cupferpulvers Phenylmercurichlorid.[28]

$$C_6H_5N_2Cl \cdot HgCl_2 + 2Ag \rightarrow C_6H_5{-}HgCl + 2AgCl + N_2$$

In diesem Falle kann aber die Reaktion nicht durch das Stadium der Bildung von metallischem Quecksilber verlaufen, da das Silber nicht imstande ist, das Quecksilber aus dem Sublimat zu verdrängen. Ganz ähnlich kann die Zersetzung von Diazoniumdoppelsalzen des Zinntetrachlorids, Bleitetrachlorids und Bleidichlorids durch Cupferpulver nicht durch das Stadium des freien Metalls verlaufen,—trotzdem führt die Zersetzung zu Zinn—und Bleiorganischen Verbindungen.

2. Wenn die Nesmejanow-Reaktion durch das Stadium der Bildung des freien Metalls verlaufen würde, müsste sie nur dort anwendbar sein, wo auch die Waters-Reaktion, die in der Wechselwirkung zwischen Aryldiazoniumchloriden und Metallen besteht, zum Ziele führt. In Wirklichkeit können die metallorganischen Verbindungen von Wismut, Tallium und Blei nur bei der Nesmejanow-Reaktion erhalten werden.

3. Die Bildung neuer Metall-Kohlenstoff-Bindungen bei der Zersetzung von Diazonium-Doppelsalzen des Aryldichlorstibins, des Aryltetrachlorstibins und des Diaryltrichlorstibins kann durch die Annahme des intermediären Auftretens von freiem Metall überhaupt nicht erklärt werden. Die Bildung von freiem Metall ist hier völlig ausgeschlossen, dabei sind diese Reaktionen nach ihrem Charakter und den Reaktionsbedingungen mit den Zersetzungsreaktionen der Metallchloriddiazoniumdoppelsalze ganz identisch.

Wenn man, dagegen, annimmt, dass die Waters-Reaktion, völlig oder grösstenteils, durch das Stadium der Doppelsalzbildung verläuft,

$$nArN_2Cl + Me \rightarrow nAr\cdot + N_2 + MeCl_n$$

$$ArN_2Cl + MeCl_n \rightarrow ArN_2^+[MeCl_{n+1}]^-$$

$$\downarrow Me$$

$$Ar{-}MeCl_{n-1}$$

so erhalten einige Beobachtungen ihre Erklärung, die bis jetzt unverständlich waren, und zwar:

1. Die Bildung des Arylmerkurichlorids aus ArN_2Cl und Quecksilber verläuft in einer wässerigen Lösung,[29] antimon oder arsen-organische Verbindungen bilden

[23] A. N. Nesmejanow *Wiss. Abhandlungen Moskauer Staatl. Univ.* N 3, 291 (1934).
[29] R. McClure u. A. Lowy *J. Amer. Chem. Soc.* **53**, 319 (1931).

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sich unter diesen Bedingungen aber nicht. Das erklärt sich dadurch, dass $SbCl_3$ und $AsCl_3$, die sich bei der Reaktion zwischen ArN_2Cl und den entsprechenden Metallen bilden,—durch das Wasser hydrolysiert werden und keine Diazoniumdoppelsalze bilden können. Das entsprechende Quecksilber-Salz wird aber nicht hydrolysiert und kann das Doppelsalz mit ArN_2Cl bilden. Dieses Doppelsalz gibt, wie wir zeigen konnten, bei der Zersetzung mit feinverteiltem Quecksilber im wässerigen Medium das Arylmerkurichlorid.

2. Es ist verständlich, warum die metallorganischen Verbindungen von Bi und Tl nur nach der Nesmejanow-Reaktion gebildet werden, die Waters-Reaktion aber versagt.

Der Grund dafür ist wahrscheinlich der, dass die Reaktion zwischen ArN_2Cl und Bi oder Tl in der Kälte nicht zustandekommt. Bei erhöhter Temperatur ist, aber, das Gleichgewicht

$$ArN_2Cl \cdot MeCl_3 \rightleftarrows ArN_2Cl + MeCl_3$$

stark nach rechts verschoben und durch das Metall wird nicht das Diazoniumdoppelsalz zersetzt, sondern das freie Aryldiazoniumhalogenid, und die Reaktion mit diesen Metallen führt nicht zur Bildung metallorganischer Verbindungen.

Es ist auch nicht verwunderlich, dass die Waters-Reaktion nicht zur Bildung von Blei-organischen Verbindungen führt, obwohl ArN_2Cl mit Blei in der Kälte reagiert: nach der Methode von Nesmejanow bilden sich die Pb-organischen Verbindungen auch nur mit winzigen Ausbeuten.

3. Wenn man anstatt des freien Aryldiazoniums die entsprechenden Zinkchlorid-Doppelsalze für die Synthese der Antimonorganischen Verbindungen verwendet,[30] so verläuft die Reaktion, wahrscheinlich, nach folgendem Schema:

$$3(C_6H_5N_2Cl)_2 \cdot ZnCl_2 + 2Sb \rightarrow 2SbCl_3 + 6C_6H_5\cdot + 3N_2 + 3ZnCl_2$$

$$(C_6H_5N_2Cl)_2 \cdot ZnCl_2 + 2SbCl_3 \rightleftarrows 2C_6H_5N_2Cl \cdot SbCl_3 + ZnCl_2$$

$$C_6H_5N_2Cl \cdot SbCl_3 \xrightarrow{Sb} \text{Sb-organische Verbindungen}$$

Wenn die Synthese Antimon-organische Verbindungen bei der Reaktion zwischen metallischem Sb und den $ZnCl_2$-Diazoniumdoppelsalzen wirklich durch das Stadium der Bildung von einem Antimontrichloriddiazonium-Doppelsalz verläuft, so muss, offensichtlich, die Zersetzung des letzteren Salzes durch das metallische Antimon zu einer höheren Ausbeute von Sb-organischen Verbindungen führen.

Waters berichtet, dass bei der Zersetzung von Zinkchloriddiazoniumdoppelsalzen die Sb-organischen Verbindungen mit einer 26%-Ausbeute erhalten werden, bei der Zersetzung von Antimontrichloriddiazoniumdoppelsalzen- nur mit einer 11%-Ausbeute. Das widerspricht unserer Auffassung.

Die Wiederholung der Versuche von Waters zeigte aber, dass er aus der Reaktionsmasse nur einen Teil der gebildeten Antimonorganischen Verbindungen—nämlich die Triaryldichlorstibine, isolierte. Die von ihm angeführten Zahlen entsprechen darum nicht der Gesamtausbeute der Sb-organischen Verbindungen. In Wirklichkeit bilden sich aus Zinkchloriddiazoniumdoppelsalzen Sb-organische Verbindungen mit einer Ausbeute von 36%, aus Antimontrichloriddiazoniumdoppelsalzen—mit einer Ausbeute von 46%.

[30] F. Makin u. W. Waters *J. Chem. Soc.* 843 (1938).

Diese Resultate stehen mit dem oben angeführten Reaktionschema im Einklang. Auch die von uns beobachtete Tatsache, dass ein Überschuss von $ZnCl_2$ die Ausbeuten erniedrigt, ist daraus verständlich.

Zur Nesmejanow-Reaktion zurückkehrend, müssen wir noch darauf hinweisen, dass die Dissoziation der Diazonium-Doppelsalze,

$$ArN_2Cl \cdot MeCl_n \rightleftarrows ArN_2Cl + MeCl_n$$

die zur Bildung von freien Arydiazoniumchlorid führt,—auf die Ausbeuten der metallorganischer Verbindungen ungünstig wirkt. Im Zusammenhang damit kann man verstehen, warum die besten Ausbeuten bei der Nesmejanow-Reaktion gewöhnlich bei der Zersetzung der Doppelsalze in der Kälte erhalten werden.

Da die Substituenten II Ordnung die Dissoziation der Metallchloriddiazoniumdoppelsalze erhöhen, so muss man zur Unterdrückung der Dissoziation (z.B. im Falle der Synthese von Quecksilberorganische Verbindungen) bis auf -10–70° abkühlen.[4]

Das geschilderte Tetsachenmaterial erlaubt uns die folgensen zwei Annahmen auszusprechen:

1. Die Zersetzung der Diazonium-Doppelsalze von Metallchloriden durch Metallpulver nach Nesmejanow, die zur Bildung von metallorganischen Verbindungen führt,—hat keinen homolytischen, sondern einen heterolytischen Charakter.

2. Die Synthese von metallorganischen Verbindungen bei der Reaktion zwischen Aryldiazoniumchloriden und Metallpulvern nach Waters verläuft durch das Stadium der intermediären Bildung von Metall-Diazonium-Doppelsalzen.

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Tetrahedron, 1957, Vol. 1, pp. 75–85. Pergamon Press Ltd., London

SYNTHÈSE DE DÉRIVÉS DE L'IMIDAZOLINO-[1,2-*c*]PYRIMIDINE ET CARACTÉRISATION DE CES PRODUITS PAR LEURS DIAGRAMMES DE POUDRE (RAYONS X)*

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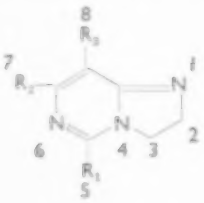
(*Received* 6 *November* 1956)

Abstract—The following imidazolino[1,2-*c*]pyrimidines



(a) R_1 = OH, SH, NH_2	R_2 = H	R_3 = NO_2
(b) R_1 = OH, SH	R_2 = NH_2	R_3 = NO_2
(c) R_1 = NH_2	R_2 = OH	R_3 = NO_2
(d) R_1 = OH, SH	R_2 = NH_2	R_3 = NH_2
(e) R_1 = OH, SH	R_2 = H	R_3 = H

have been synthesised according to scheme A (I → VI, p. 76) or scheme B (VIII → XV, p. 78).

Compounds

(a) R_1 = OH, R_2 = H, R_3 = NO_2,

(b) R_1 = OH, R_2 = NH_2, R_3 = NO_2,

(b) R_1 = SH, R_2 = NH_2, R_3 = NO_2

and

(c) R_1 = SH, R_2 = H, R_3 = H

have no effect on the growth of tobacco mosaic virus.

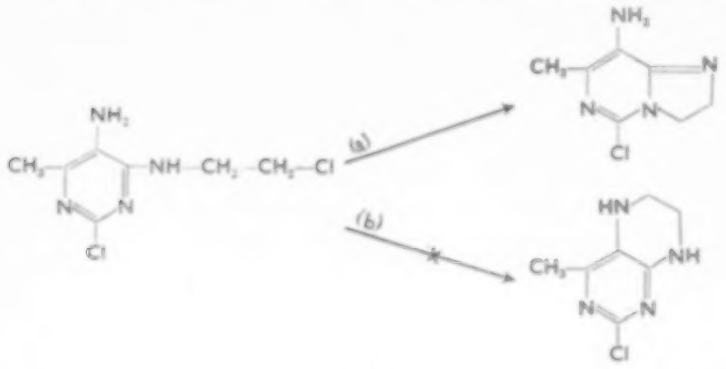
The final products are characterised by their X-ray powder diffraction patterns. It is suggested that this simple method of identification should be used systematically in the case of compounds which do not melt sharply.

AU cours de leurs recherches sur la synthèse de dérivés ptéridiques, Ramage et Trappe[1] ont montré qu'une chaîne 2-chloroéthylaminée fixée en position 4 dans un noyau pyrimidique cyclise facilement sur l'atome d'azote nucléaire pour donner une imidazolino[1,2-*c*]pyrimidine. On constate donc que le cyclisation (a) l'emporte sur

* Une partie de ce travail a fait l'objet d'une communication préliminaire au 14e Congrès International de Chimie Pure et Appliquée (Zurich, Juillet 1955).

[1] G. R. Ramage et G. Trappe *J. Chem. Soc.* 4410 (1952).

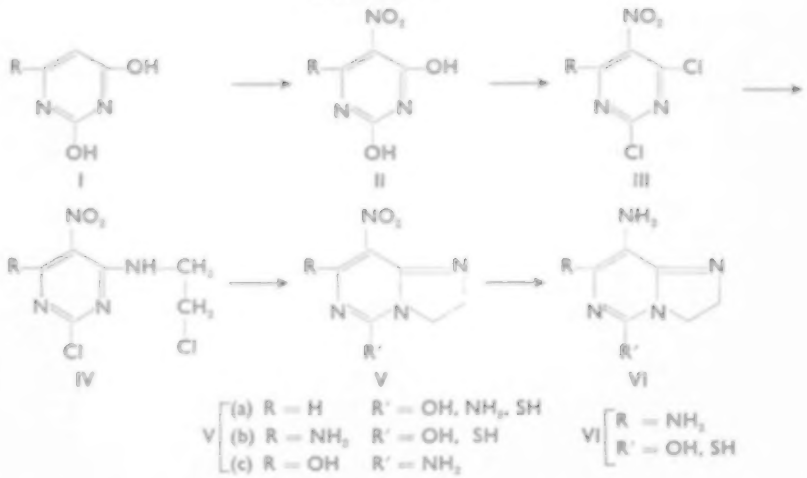
celle mettant en jeu la fonction amine présente en position 5 (cyclisation b).



I

Dans le but de préparer de nouveaux dérivés de l'imidazolino[1,2-*c*]pyrimidine, nous nous sommes inspirés des résultats de ces auteurs et avons réalisé le schéma de synthèse suivant:

SCHEMA A



(a) R = H. La nitration de l'uracile (préparé selon la méthode de Davidson[2]) peut être réalisée par action d'un mélange d'acides nitrique et sulfurique[3] ou par l'acide nitrique seul.[4] Nous avons appliqué successivement:

(1) la méthode de Köhler[3] par l'acide sulfonitrique (rendement : 45%)
(2) la méthode de Boon, Jones, et Ramage[5] qui, dans le cas de la nitration de la 4,6-dihydroxypyrimidine par un mélange d'acides nitrique et acétique, donne 90% de rendement. Cette méthode a malheureusement échoué au départ d'uracile.

[2] D. Davidson et O. Baudish *J. Amer. Chem. Soc.* **48**, 2379 (1926).
[3] A. Köhler *Ann.* **236** 50 (1886).
[4] T. B. Johnson et I. Matsuo *J. Amer. Chem. Soc.* **41**, 783 (1919).
[5] W. R. Boon, W. G. Jones, et G. R. Ramage *J. Chem. Soc.* 96 (1951).

(3) la méthode de Johnson et Matsuo,[4] par action d'acide nitrique fumant, à 50–60°, nous a fourni le nitrouracile avec un rendement quantitatif.

Le 5-nitrouracile ainsi obtenu est ensuite traité par un mélange d'oxychlorure de phosphore et de diméthylaniline[6] pour donner la 2,4-dichloro-5-nitropyrimidine avec 68% de rendement. La distillation de ce composé s'avère assez délicate, celui-ci se décomposant très violemment lorsque la température du bain atteint 195°.

L'aminolyse sélective en position 4 de la 2,4-dichloro-5-nitropyrimidine est réalisée au moyen de la 2-chloréthylamine, en présence de bicarbonate de sodium, avec un rendement de 96%. La sélectivité d'aminolyse a été mise en évidence par plusieurs auteurs dans des cas analogues.[5,7,8,9]

A partir de cette 2-chloro-4-(2-chloréthyl)amino-5-nitropyrimidine (IV), il est possible d'effectuer simultanément la cyclisation de la chaîne chloraminée et la substitution du chlore en position 2. Trois produits finaux nouveaux ont pu être préparés de la façon suivante:

(1) V (R = H, R′ = OH) hydrolyse acide du chlore en 2, accompagnée de cyclisation;

(2) V (R = H, R′ = NH_2) ammonolyse au moyen d'ammoniac alcoolique, suivie de cyclisation en milieu aqueux;

(3) V (R = H, R′ = SH) cyclisation et hydrolyse par la soude du sel de thiouronium en 2, obtenu par action de la thiourée en milieu acétonique.

(b) R = NH_2. Ce schéma a été répété sur la 4-amino-2,6-dihydroxypyrimidine comme produit de départ. Cette pyrimidine (I), préparée par condensation de cyanacétate d'éthyle et d'urée en milieu éthanol-éthylate de sodium,[10] est ensuite nitrée par un mélange d'acides nitrique et sulfurique,[8] puis chlorée par l'oxychlorure de phosphore en présence de diméthylaniline. La monoaminolyse (IV) et les cyclisations (V) sont alors effectuées comme dans le cas précédent.

L'hydrolyse acide et la cyclisation d'une part, la sulfuration par la thiourée d'autre part, réalisées sur le dérivé (IV) (R = NH_2), ont conduit aux produits normalement attendus : V (R = NH_2, R′ = OH) et V (R = NH_2, R′ = SH).

Par contre, l'ammonolyse ne nous a pas permis d'isoler V (R = NH_2, R′ = NH_2), mais bien (R = OH, R′ = NH_2). Cette hydrolyse assez exceptionnelle de la fonction amine en ortho du groupe nitro a été prouvée avec certitude. Une réduction du groupe nitro au moyen d'hydrosulfite de sodium en milieu ammoniacal nous a fourni les deux composés VI (R = NH_2, R′ = OH) et VI (R = NH_2, R′ = SH).

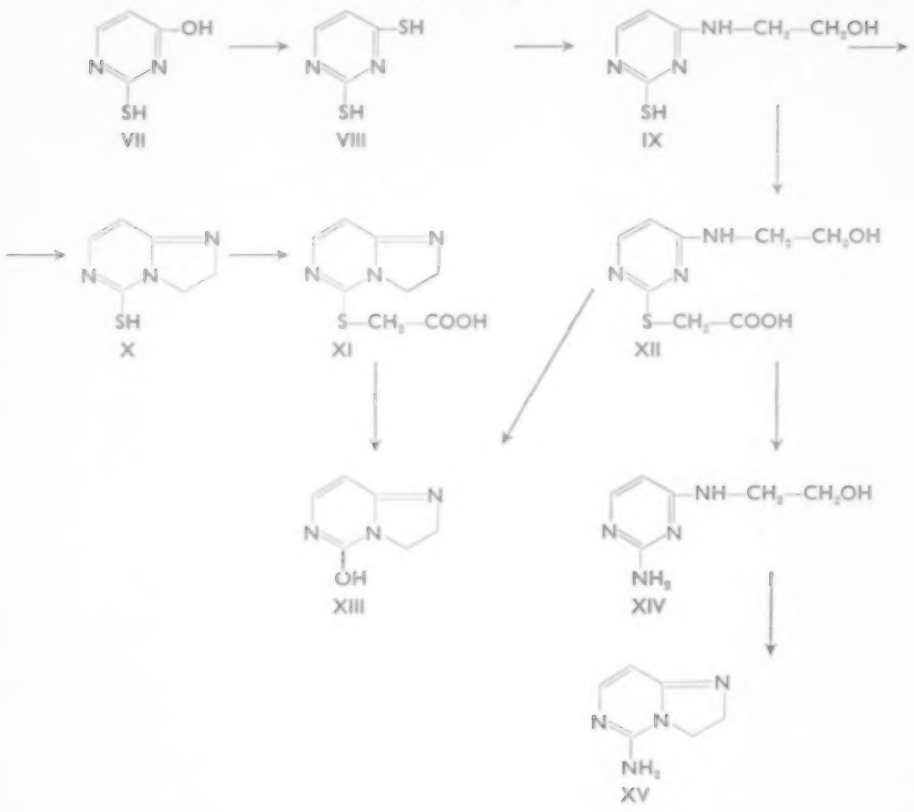
II

Nous avons mis au point un second schéma de synthèse qui diffère du premier par le mode de fixation de la chaîne latérale aminée sur le noyau pyrimidique, ainsi que par la méthode de cyclisation de cette chaîne sur l'atome d'azote nucléaire de la pyrimidine.

[6] N. Wittaker *J. Chem. Soc.* 1565 (1951).
[7] W. R. Boon et W. G. M. Jones *J. Chem. Soc.* 591 (1951).
[8] P. Bitterli et H. Erlenmeyer *Helv. Chim. Acta.* **34,** 837 (1951).
[9] D. J. Brown *J. Appl. Chem.* **2,** 239 (1952).
[10] M. Conrad *Ann.* **304,** 312 (1905).

Cette suite de réactions peut être représentée par le schéma suivant:

SCHEMA B



Le thiouracile, obtenu avec 40% de rendement par condensation de formylacétate d'éthyle sur la thiourée, est traité par le pentasulfure de phosphore dans la pyridine comme solvant. Celle méthode, due à Klingsberg et Papa,[11] donne de meilleurs rendements que celle utilisant la tétraline comme solvant[12] (75–80% au lieu de 65%).

L'aminolyse de la 2,4-dimercaptopyrimidine au moyen d'éthanolamine conduit à la 4-(2-hydroxyéthyl)amino-2-mercaptopyrimidine (IX) avec 80% de rendement.[13]

Cette dernière pyrimidine est traitée par le chlorure de thionyle, et, après évaporation du réactif, la 4(2-chloréthyl)amino-2-mercaptopyrimidine brute est chauffée à reflux dans l'eau. Cette solution est ensuite neutralisée par du bicarbonate de sodium afin de précipiter le produit cyclisé (X). L'ensemble des deux réactions (chloruration et cyclisation) est effectuée avec 62% de rendement.

La 5-hydroxy-imidazolino[1,2-*c*]pyrimidine a été préparée de deux manières différentes à partir de la 4(2-hydroxyéthyl)amino-2-mercaptopyrimidine (IX). La

[11] E. Klingsberg et D. Papa *J. Amer. Chem. Soc.* **73**, 4988 (1951).
[12] G. B. Elion et G. H. Hitchings *J. Amer. Chem. Soc.* **69**, 2138 (1947).
[13] P. B. Russel, G. B. Elion, E. A. Falco, et G. H. Hitchings *J. Amer. Chem. Soc.* **71**, 2279 (1949).

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première voie, qui consiste à cycliser la chaîne latérale fixée en 4, puis à hydrolyser le groupe mercapto (IX—XIII), donne un rendement global de 26%. La seconde méthode, qui consiste à traiter la 2-carboxyméthylthio-4(2-hydroxyéthyl)amino-pyrimidine par l'acide bromhydrique azéotropique, permet d'obtenir le dérivé XIII avec un rendement global de 59% (IX→XII→XIII). On réalise ainsi trois réactions en une seule opération: hydrolyse du groupe carboxyméthylthio, bromuration de la chaîne latérale fixée en 4, et cyclisation de cette dernière sur l'azote nucléaire.

La 2-carboxyméthylthio-4-(2-hydroxyéthyl)amino-pyrimidine a également été convertie en 2-amino-4-(2-hydroxyéthyl)amino-pyrimidine, par action d'ammoniaque en tube scellé à 140° (rendement: 80%). Cette dernière pyrimidine, traitée par l'acide bromhydrique azéotropique, a permis d'isoler un dérivé qui doit être la 5-amino-imidazolino[1,2-*c*]pyrimidine (XV). Toutefois, la structure du produit obtenu par cette réaction n'a pu être déterminée avec certitude.

La préparation de nouveaux dérivés de l'imidazolino[1,2-*c*]pyrimidine, ainsi que celle du système cyclique fondamental sans aucun substituant, est actuellement poursuivie dans nos laboratoires.

III

DIAGRAMMES DE RAYONS X (MÉTHODE DES POUDRES)

Aucun des dérivés de l'imidazolino[1,2-*c*]pyrimidine que nous avons préparés n'a de point de fusion net. Toutes ces substances se décomposent à des températures supérieures à 300° et dans un intervalle de 20 à 30°. Il nous a dès lors paru important de les caractériser par une autre méthode physique.

Nous avons établi les diagrammes de rayons X de tous nos produits finaux par la méthode des poudres (Debye-Scherrer) en utilisant la radiation CuK_{α_1} filtrée (filtre de nickel). Ce mode de caractérisation s'est révélé particulièrement intéressant, car il n'exige qu'une très petite quantité de produit (2 à 3 mg) facilement récupérable; le degré de pureté de l'échantillon ne doit pas être très élevé (90–95%) et l'on obtient en outre des diagrammes comportant en moyenne 10 anneaux nettement marqués et dont les positions diffèrent totalement d'un produit à l'autre, même lorsque leurs structures sont très voisines (par exemple, deux isomères de position).

Nous suggérons que cette méthode simple d'identification soit utilisée systématiquement dans le cas des dérivés qui n'ont pas de point de fusion caractéristique.

On trouvera ci-dessous les tableaux mentionnant les valeurs des équidistances d (exprimées en Å) et des intensités relatives (I_r) des bandes correspondant à ces équidistances.

1 7-amino-5-hydroxy-8-nitro-imidazolino[1,2-*c*]pyrimidine
2 5-amino-7-hydroxy-8-nitro-imidazolino[1,2-*c*]pyrimidine
3 7-amino-5-mercapto-8-nitro-imidazolino[1,2-*c*]pyrimidine
4 7,8-diamino-5-mercapto-imidazolino[1,2-*c*]pyrimidine
5 picrate de la 7,8-diamino-5-hydroxy-imidazolino[1,2-*c*]pyrimidine
6 5-hydroxy-8-nitro-imidazolino[1,2-*c*]pyrimidine
7 picrate de la 5-hydroxy-8-nitro-imidazolino[1,2-*c*]pyrimidine
8 5-amino-8-nitro-imidazolino[1,2-*c*]pyrimidine
9 5-mercapto-8-nitro-imidazolino[1,2-*c*]pyrimidine

10 5-mercapto-imidazolino[1,2-*c*]pyrimidine
11 picrate de la 5-hydroxy-imidazolino[1,2-*c*]pyrimidine
12 picrate de la 2-amino-4(2-hydroxyéthyl)aminopyrimidine
13 picrate du produit (XV) obtenu par action d'acide bromhydrique sur la 2-amino-4(2-hydroxyéthyl)aminopyrimidine.

$CuK_{\alpha_1} = 1,5405_0$
Temps de pose: 3 à 4 heures
Rayon de la chambre: 5 cm
I_r: VL = very light (très faible intensité)
L = light (faible intensité)
M = medium (intensité moyenne)
S = strong (forte intensité)
VS = very strong (très forte intensité)

1

	d	I_r
1	8,10	L
2	6,57	VL
3	4,12	VL
4	3,78	VS
5	3,12	M
6	2,94	L
7	2,69	M
8	3,26	VL

2

	d	I_r
1	7,50	M
2	6,42	L
3	5,94	L
4	3,72	L
5	3,42	S
6	3,20	L
7	2,71	VL
8	2,52	VL
9	2,25	VL
10	2,14	VL

3

	d	I_r
1	9,00	S
2	7,69	VL
3	7,01	M
4	5,33	L
5	4,76	L
6	3,77	VL
7	3,65	VL
8	3,34	VS
9	2,97	VL

4

	d	I_r
1	7,49	L
2	6,90	L
3	5,07	VL
4	3,93	M
5	3,37	S
6	2,76	VL
7	2,57	VL
8	2,26	VL
9	2,17	VL

5

	d	I_r
1	11,45	VL
2	7,80	S
3	6,85	VL
4	6,41	L
5	5,06	M
6	4,12	VL
7	3,73	VS
8	3,56	L
9	3,27	L
10	3,08	VL
11	2,90	L
12	2,63	VL

6

	d	I_r
1	7,80	S
2	6,70	VL
3	5,42	VL
4	4,63	M
5	3,93	VL
6	3,58	L
7	3,27	VS
8	3,02	VL

7

	d	I_r
1	8,11	L
2	7,13	L
3	6,28	L
4	5,52	VL
5	5,05	M
6	4,69	M
7	4,27	L
8	3,88	VL
9	3,53	VL
10	3,50	S
11	3,13	M

8

	d	I_r
1	10,51	M
2	7,30	L
3	6,50	S
4	4,66	VL
5	3,80	M
6	3,40	VS
7	2,97	VL
8	2,64	VL
9	2,37	VL
10	2,30	VL
11	1,71	VL

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9

	d	I_r
1	7,60	L
2	6,74	VL
3	6,28	VL
4	4,55	VL
5	3,90	L
6	3,53	M
7	3,28	VL
8	2,92	VL

10

	d	I_r
1	7,56	M
2	6,55	VL
3	5,33	VL
4	4,84	L
5	4,48	M
6	3,37	S
7	3,18	VL
8	2,42	VL

11

	d	I_r
1	11,32	VL
2	6,32	L
3	4,55	M
4	4,36	VL
5	4,03	L
6	3,73	VS
7	3,57	VL
8	3,42	L
9	3,20	S

12

	d	I_r
1	11,04	VL
2	7,67	M
3	6,20	VL
4	5,60	VL
5	4,97	L
6	4,61	L
7	3,83	VL
8	3,42	S

13

	d	I_r
1	8,66	VL
2	7,82	VL
3	6,75	L
4	4,77	L
5	4,48	L
6	4,15	L
7	3,77	M
8	3,53	S
9	3,32	M
10	3,17	VL

PARTIE EXPERIMENTALE

2-Chloro-4(2-chloréthyl)amino-5-nitropyrimidine (IV, R = H)

On dissout 19,4 g (0,1 m) de 2,4-dichloro-5-nitropyrimidine dans 150 ml d'éther. On ajoute une solution aqueuse de 14 g de chlorhydrate de 2-chloréthylamine et de 24 g de bicarbonate de sodium. Les deux phases, aqueuse et éthérée, sont intimement brassées au moyen d'un vibromoteur. La phase éthérée est décantée et la couche aqueuse est extraite à l'éther. Les phases éthérées réunies sont lavées une fois à l'eau, puis séchées sur sulfate de sodium. Après évaporation de l'éther, l'huile résiduelle cristallise en aiguilles jaunes. On isole après recristallisation dans le cyclohexane 22,8 g (0,096 m) de 2-chloro-4(2-chloréthyl)amino-5-nitropyrimidine fondant à 72–73°. Rendement : 96%.

4-Amino-2-chloro-6(2-chloréthyl)amino-5-nitropyrimidine (IV, R = NH_2)

9 g (0,043 m) de 4-amino-2,6-dichloro-5-nitropyrimidine sont traités comme dans la préparation précédente. Après deux heures d'agitation à 0–10°, on isole 10,5 g (0,042 m) du produit désiré, se décomposant à 300–310°. Rendement: 97%.

5-Hydroxy-8-nitro-imidazolino[1,2-c]pyrimidine (V, R = H, R′ = OH)

0,65 g (0,0027 m) de 2-chloro-4(2-chloréthyl)amino-5-nitropyrimidine et 10 ml d'eau sont chauffés à reflux jusqu'à dissolution totale. La solution jaune est alors neutralisée par du bicarbonate de sodium. On laisse reposer la solution à 0° pendant 4 heures. Le précipité formé est filtré, lavé et séché. On isole ainsi 0,32 g (0,00175 m) du produit cherché. Point de décomposition: 260–270°. Rendement: 64%.

$C_6H_6O_3N_4$ (182) Calculé C: 39,6 H: 3,2 N: 30,8

Trouvé C: 39,3 H: 3,4 N: 30,9

Picrate: $C_{12}H_9O_{10}N_7$ (411)

Calculé C: 35,0 H: 2,2 N: 23,8

Trouvé C: 34,9 H: 2,0 N: 24,2

Point de décomposition du picrate (recristallisé dans l'eau): 210–220°.

5-Amino-9-nitro-imidazolino[1,2-c]pyrimidine (V, R = H, R′ = NH_2)

Une solution alcoolique de 0,7 g (0,003 m) de 2-amino-4(2-chloréthyl)amin o-5 nitropyrimidine est traitée par 10 ml d'ammoniac alcoolique. Après 2 heures à température ordinaire et 2 heures à 0°, on filtre le précipité formé. Celui-ci est dissous dans l'eau à chaud et cette solution (acide) est neutralisée par du bicarbonate de sodium. Il se forme 0,37 g (0,0018 m) d'aiguilles jaunes. Rendement: 60%. Ce produit, recristallisé dans l'eau, a un point de décomposition de 205–220°.

$C_6H_7O_2N_5 + H_2O$ (200)

Calculé C: 36,2 H: 4,5 N: 35,2

Trouvé C: 36,1 H: 4,4 N: 35,3

Analyse de l'eau de cristallisation : Calculé: 9,0

Trouvé: 9,2

5-Mercapto-9-nitro-imidazolino[1,2-c]pyrimidine (V, R = H, R′ = SH)

On dissout dans une solution de soude le sel de thiouronium obtenu après une heure de chauffage à reflux d'une solution acétonique de 1 g (0,0042 m) de pyrimidine de départ (IV, R = H) et de 0,36 g (0,0049 m) de thiourée. Cette solution basique est chauffée pendant 3 minutes, puis est acidifiée par l'acide acétique. On isole ainsi 0,55 g (0,0025 m) de 5-mercapto-8-nitro-imidazolino[1,2-c]pyrimidine.

La recristallisation dans l'eau fournit des aiguilles jaune-rouge. Point de décomposition: 230–240°. Rendement: 60%.

$C_6H_6O_2N_4S + H_2O$ (216) Calculé C: 33,3 H: 3,7 N: 25,9

Trouvé C: 33,8 H: 3,7 N: 25,4

7-Amino-5-hydroxy-8-nitro-imidazolino[1,2-c]pyrimidine (V, R = NH_2, R′ = OH)

Une suspension de 0,5 g (0,002 m) de 4-amino-2-chloro-6(2-chloréthyl)amino-5-nitropyrimidine dans 8 ml d'acide chlorhydrique 5 N est chauffée à reflux. Après 5

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minutes, la dissolution est totale; après 10 minutes, un nouveau précipité blanc se forme; on laisse refroidir après 15 minutes. Le précipité est filtré puis redissous dans l'eau à chaud. La solution est neutralisée par du bicarbonate de sodium. Il se forme un nouveau solide blanc (0,32 g, soit 0,00164 m). Rendement: 82%. Le produit recristallise dans l'eau en aiguilles blanches. Point de décomposition: 330–340°.

$C_6H_7O_3N_5$ (197)

Calculé	C: 36,6	H: 3,6	N: 35,5
Trouvé	C: 36,6	H: 3,8	N: 35,3

7-Amino-5-mercapto-8-nitro-imidazolino[1,2-c]pyrimidine (V, R = NH_2, R′ = SH)

On chauffe 3 heures à reflux une solution acétonique de 3 g (0,012 m) de 4-amino-2-chloro-6(2-chloréthyl)amino-5-nitropyrimidine et de 1,25 g de thiourée (0,016 m). On filtre 4,1 g du sel de thiouronium formé, puis on le dissout à chaud dans 100 ml de soude N. Par acidification à l'acide acétique, on obtient 1,47 g (0,0069 m) du produit cyclisé cherché. Ce produit est purifié par plusieurs dissolutions dans la soude et reprécipitations au moyen d'acide acétique. Rendement: 58%.

$C_6H_7O_2N_5S$ (213)

Calculé	C: 33,8	H: 3,3	N: 32,9
Trouvé	C: 33,6	H: 3,5	N: 32,4

5-Amino-7-hydroxy-8-nitro-imidazolino[1,2-c]pyrimidine (V, R = OH, R′ = NH_2)

3 g (0,012 m) de 4-amino-2-chloro-6(2-chloréthyl)amino-5-nitro-pyrimidine sont dissous dans 150 ml d'acétone; après addition de 150 ml d'acétone ammoniacale, le tout est laissé un jour et une nuit à 0°. Le précipité formé est filtré puis chauffé une heure à reflux dans 90 ml d'eau. Après addition de bicarbonate de sodium, on isole 1,10 g (0,0056 m) d'aiguilles oranges qui sont recristallisées dans l'eau. Rendement: 47%. Point de décomposition: 320–340°.

$C_6H_7O_3N_5$ (197)

Calculé	C: 36,6	H: 3,6	N: 35,5
Trouvé	C: 36,5	H: 3,6	N: 35,4

7,8-Diamino-5-hydroxy-imidazolino[1,2-c]pyrimidine (VI, R = NH_2, R′ = OH)

Une suspension de 0,4 g (0,002 m) du dérivé 8-nitré (V, R = NH_2, R′ = OH) dans 10 ml d'ammoniaque contenant 2,4 g de dithionite de sodium est chauffée à reflux. Après 10 minutes, le produit est complètement dissous et la solution ainsi obtenue est filtrée à chaud, puis neutralisée. On laisse reposer une nuit à 0° et on isole 0,24 g (0,0014 m) d'aiguilles jaunâtres. Rendement: 70%.

Picrate: $C_{12}H_{12}O_8N_8$ (396)

Calculé	C: 36,4	H: 3,1	N: 28,3
Trouvé	C: 36,8	H: 3,2	N: 28,4

Point de décomposition du picrate (recristallisé dans l'eau): 245–248°.

Ce produit a également été obtenu par hydrogénation catalytique dans le méthanol en présence de nickel de Raney à pression et température ordinaires.

7,8-Diamino-5-mercapto-imidazolino[1,2-c]pyrimidine (VI, R = NH_2, R′ = SH)

On traite 0,21 g (0,001 m) du dérivé 8-nitré (V, R = NH_2, R′ = SH) par 3 ml d'ammoniaque et 1,2 g de dithionite de sodium. On isole 0,13 g (0,0007 m) du produit 8-aminé. Rendement: 70%. Point de décomposition: entre 270 et 292° (fond à 330–335°)

$C_6H_9N_5S$ (183)

Calculé	C: 39,3	H: 5,0	N: 38,2
Trouvé	C: 39,2	H: 4,9	N: 37,7

Ce produit est recristallisable dans l'eau.

5-Mercapto-imidazolino[1,2-c]pyrimidine (X)

On chauffe à reflux pendant 5 minutes un mélange de 2 g (0,0117 m) de 4-(2-hydroxyéthyl)amino-2-mercaptopyrimidine et de 5 ml de chlorure de thionyle. Ce dernier est ensuite chassé sous vide et 20 ml d'eau sont ajoutés au résidu. On acidifie par 2 ou 3 ml d'acide chlorhydrique et la solution est alors chauffée pendant une heure à reflux. Les impuretés insolubles sont séparées par filtration à chaud et le filtrat est neutralisé par du bicarbonate de sodium. On isole ainsi 1,12 g (0,0073 m) de produit. Rendement: 62%. Point de décomposition: 310–315°.

$C_6H_7N_3S$ (153)

Calculé	C: 47,0	H: 4,6	N: 27,4
Trouvé	C: 47,0	H: 4,7	N: 27,1

5-Carboxyméthylthio-imidazolino[1,2-c]pyrimidine (XI)

1,8 g (0,012 m) de 5-mercapto-imidazolino[1,2-*c*]pyrimidine est mis en suspension dans 5 ml d'eau. On ajoute 1,12 g (0,012 m) d'acide chloracétique dans 5 ml d'eau. On chauffe jusqu'à dissolution complète (5 minutes) puis on concentre jusqu'à 2 à 3 ml. Le précipité qui se forme, filtré et séché, pèse 1,5 g (0,0072 m). Rendement: 60%.

2-Carboxyméthylthio-4(2-hydroxyéthyl)aminopyrimidine (XII)

5,1 g de 4(2-hydroxyéthyl)amino-2-mercaptopyrimidine sont mis en suspension dans 15 ml d'eau. On ajoute 2,84 g (0,03 m) d'acide chloracétique dans 10 ml d'eau. Après 5 minutes de chauffage à reflux, il y a dissolution. La solution jaune clair est filtrée à chaud, puis évaporée jusqu'à début de précipitation. On laisse refroidir puis on filtre le précipité formé et on le lave à l'acétone. On isole ainsi 6,7 g (0,0293) de produit blanc fondant à 169–170°. Rendement: 98%.

5-Hydroxy-imidazolino[1,2-c]pyrimidine (XIII)

1ère *méthode*. 0,45 g (0,0021 m) de 5-carboxyméthylthio-imidazolino[1,2-*c*] pyrimidine (XI) et 8 ml d'acide chlorhydrique sont chauffés en tube scellé à 140° pendant 3 heures. On évapore ensuite la moitié de la solution, puis on ajoute 10 ml d'alcool éthylique. On obtient ainsi 0,26 g (0,0015 m) de chlorhydrate du produit désiré. Rendement: 71%.

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Picrate : $C_{12}H_{10}O_8N_6$ (366)

Calculé	C: 39,4	H: 2,8	N: 23,0	O: 35,0
Trouvé	C: 39,6	H: 2,7	N: 22,9	O: 34,9

Point de décomposition du picrate: 228–230°.

2ème méthode. On chauffe à reflux pendant 5 heures une solution de 2 g (0,0087 m) de 2-carboxyméthylthio-4(2-hydroxyéthyl)amino-pyrimidine (XII) dans 10 ml d'acide bromhydrique azéotropique. On évapore ensuite environ les 2/3 de la solution, puis on ajoute 15 ml d'alcool éthylique. Il se sépare alors 1,12 g de cristaux blancs (0,0051 m) Rendement: 59%. Point de décomposition du picrate: 228–230°.

Picrate : Trouvé C: 39,2 H: 2,8 N: 22,9 O: 34,7

2-Amino-4(2-hydroxyéthyl)amino-pyrimidine (XIV)

2 g de 2-carboxyméthylthio-4(2-hydroxyéthyl)amino-pyrimidine (0,0087 m) sont traités par 26 ml d'ammoniaque en tube scellé, à 145–150° pendant 24 heures. Les 2/3 de la solution sont ensuite évaporés, et après addition de 10 ml de soude à 40%, on isole 1,09 g (0,0071 m) du produit désiré. Rendement en produit brut: 81%.

Picrate : $C_{12}H_{13}O_8N_7$ (383)

Calculé	C: 37,6	H: 3,4	N: 25,6	O: 33,4
Trouvé	C: 37,3	H: 3,4	N: 25,6	O: 33,1

Point de fusion du picrate: 175–177°.

Les produits (V, R = H, R′ = OH), (V, R = NH_2, R′ = SH), (V, R = NH_2, R′ = OH), et (XI) ont été testés sur le virus de la mosaïque du tabac et se sont révélés sans action inhibitrice sur le développement de ce virus.

Nous remercions Monsieur le Professeur R. Jeener et Madame Van Rysselberghe qui ont effectué ces essais biologiques.

Nous tenons en outre à exprimer notre gratitude à l'Institut pour l'encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture (I.R.S.I.A.) et le Fonds National Belge de la Recherche Scientifique (F.R.N.S.) pour l'aide materielle qu'ils nous ont accordée et qui nous a permis de mener à bien ce travail.

Note ajoutée lors de la correction des épreuves (10 *mars* 1957):

(1°) Nous avons récemment trouvé que la 5-mercapto-imidazolino[1,2-*c*]pyrimidine(X) et la 7-amino-5-mercapto-8-nitro-imidazolino[1,2-*c*]pyrimidine(V) (R = NH_2, R′ = SH) cristallisent très bien dans la diméthylformamide [Trouvé: (X) C = 47,3; H = 4,6; (V) (R = NH_2, R′ = SH) C = 34,0; H = 3,4].

(2°) Nous exprimons notre très vive reconnaissance au Professeur Dr. Sydney Farber, Directeur de la "Children's Cancer Research Foundation" (Boston) grâce à qui les composés (V) (R = H, R′ = OH) et (V) (R = NH_2, R′ = OH) ont pu être soumis dernièrement à de sérieux tests sur diverses tumeurs expérimentales. Ces deux dérivés se sont avérés inactifs dans tous les cas étudiés.

Tetrahedron, 1957, Vol. 1, pp. 86–102. Pergamon Press Ltd., London

RECENT DEVELOPMENT IN THE SYNTHESIS AND STEREOCHEMISTRY OF TROPANE ALKALOIDS

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(*Received* 19 *March* 1957)

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Abstract—Two years ago several comprehensive reviews [1,2,3,4] on the stereochemistry of tropane alkaloids which dealt with earlier and more recent results were presented. Since then, however, an additional number of findings and, in particular, some stereospecific syntheses have been recorded in this field. Accordingly, it is deemed of interest to give an account of recent developments.

The main features of most of the recent research are as follows:

1. Stereospecific syntheses of some new epimeric ecgoninols and ecgonines as well as that of scopolamine, valeroidine, dihydrometeloidine, oscine.
2. Establishing of the configuration of the nitrogen atom in tertiary amines and quaternary salts of the tropane series related to (−)ecgoninol, (±)3α-6β-dihydroxy-tropane and (±)oscine.
3. Enol isomerism and ring opening in the tropines.
4. Investigations and considerations concerning the structure of dioscorine.
5. Recent stereochemical aspects of the problem of biogenesis of scopolamine and hyoscyamine.

1. STEREOSPECIFIC SYNTHESES

(a) *Synthesis of some new ecgoninols and ecgonines*

SYNTHESIS of the hitherto unknown third and fourth racemic cocaines, and of the fourth ecgonine racemate as well as their optically active components has been attempted on different lines.

Chronologically: first the synthesis of two new epimers of 2-hydroxymethyl-tropan-3-ols (2β-hydroxymethyl-3α-tropanol, and of 2α-hydroxymethyl-3α-tropanol) has been realised in order to submit, subsequently, these diols to selective oxidation. Another line of approach dealing with the third racemate of ecgonine ester arising from hydrogenation of methyl tropinone-2-carboxylate has, according to Willstätter, been converted into the corresponding cocaine, while epimerisation of the third racemic ester led to the fourth racemic ecgonine methyl-ester, which in turn has been benzoylated to the fourth (±)cocaine.

(−)2β-Chloromethyl-3β-tropanol underwent rearrangement into the hydrochloride of a base to which several alternative structures, envisaged in previous papers[3,5] could be allotted initially. The choice among them in favour of the structure of 2′,3-anhydro-2β-hydroxymethyl-3β-tropanol was made possible by the following facts (Fig. 1):

(1) 2β-chloromethyl-3β-acetoxy-tropane failed to undergo rearrangement, showing the participation of the C_3-OH group in this reaction.[5]

(2) The hydrochloride of the base has been reconverted by hydrochloric acid into the chloromethyl derivative from which we started.[5]

[1] A. Stoll and E. Jucker *Angew. Chem.* **66**, 376 (1954).
[2] E. Jucker *Chimia* **9**, 25 (1955).
[3] G. Fodor *Acta Chim. Acad. Sci. Hungar.* **5**, 379–442 (1955).
[4] G. Fodor *Exper.* **11**, 129–141 (1955).
[5] Ö. Kovács, G. Fodor, and I. Weisz *Helv. Chim. Acta* **37**, 892 (1954).

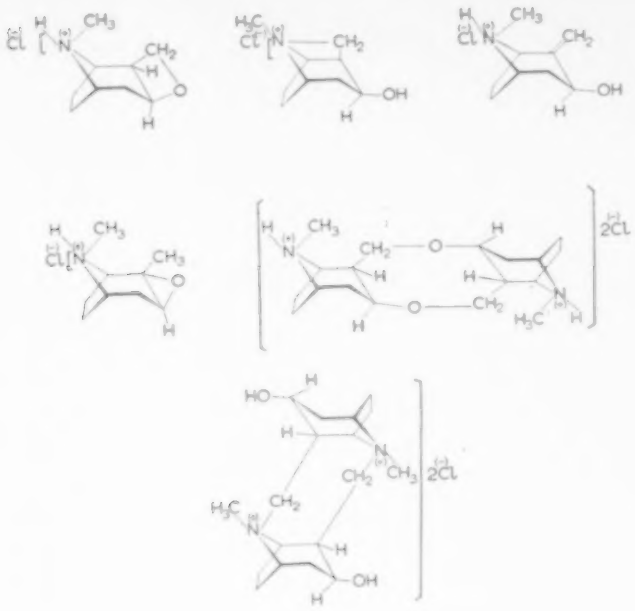

FIG. 1.

(3) The molecular weight of the compound has been found[6] by the ebullioscopic method, 197·5 as an average.

(4) The rate of the rearrangement has been determined both by polarimetric and argentometrical methods,[6] indicating independence of rate from concentration, i.e. pointing to a truly unimolecular mechanism.

(5) Methiodide of 2β-chloromethyl-3β-tropanol[6] underwent similar rearrangement, but in the presence of a molecule of alkali to give the methiodide of the cyclic ether. The methochloride of this latter has been reconverted by acetyl chloride in acetic anhydride into the acetyl derivative of 2β-chloromethyl-3β-tropanol methochloride.

(6) Ring cleavage of the cyclic ether itself has been achieved either by acetic anhydride or alkali. The first reactant gave rise to a mixture of diacetyl ecgoninols: 2β-acetoxymethyl-3β-acetoxy tropane, besides the dominating epimeric modification which can only be its 3α-isomer. Hydrolysis of these diacetates gave rise to 2β-hydroxymethyl-3β-tropanol and to the new ecgoninol, 2β-hydroxymethyl-3α-tropanol. Action of hydroxyl ions on the ether ring led to the same epimers. The 3α-modification may be formed only by means of a nucleophilic attack of hydroxyl ions towards the asymmetric bridgehead of the ether ring. This reaction showed indeed a pure bimolecular course, its point of attack being carbon atom No. 3. Further evidence in favour of the four-membered ring ether structure has been provided by infra-red spectroscopic investigations—in collaboration with Basle University[6]—of the compound in play, comparing their curves with those of trimethylene oxides.[7] These results may serve as the first contributions to the stereochemistry of formation and cleavage of

[6] Ö. Kovács, I. Weisz, P. Zoller, and G. Fodor *Ibid.* **39**, 99 (1956).
[7] G. M. Barrow and S. Searles *J. Amer. Chem. Soc.* **75**, 1175 (1953).

four-membered ring ethers. Another paper[8] dealing with the stereochemistry of the cleavage of a 1·3-oxido-bridged *cyclo*hexane appeared formerly as the single precursor in this field. The reactions carried out with electrophilic and nucleophilic reactants mainly show a close resemblance with the steric course of the cleavage of epoxides[6] while the four-membered ring ether resists catalytic hydrogenolysis at variance with epoxides.

Authentic 2β-hydroxymethyl-3α-tropanol has thus been obtained, the absolute configuration of which being given by the correlation of (−)cocaine with L(+) glutamic acid according to Hardegger and Ott[9] (Fig. 3a).

As a further step, this could be converted by sodium amyloxide and benzophenone as a catalyst by way of a half cell oxidation reduction[10] procedure into a hitherto unknown tropandiol to which the structure of 2α-hydroxymethyl-3α-tropanol could be allotted, due to inversion at C_2 only, since otherwise epimerisation of the starting material at C_3 would lead to ecgoninol, while affection of both C_2 and C_3 centres should give ψ-ecgoninol. Hence the "exclusion principle" supports this configuration.[6] Oxidation experiments have in turn been commenced with all the four 2-hydroxymethyl-3-tropanols (Fig. 2).

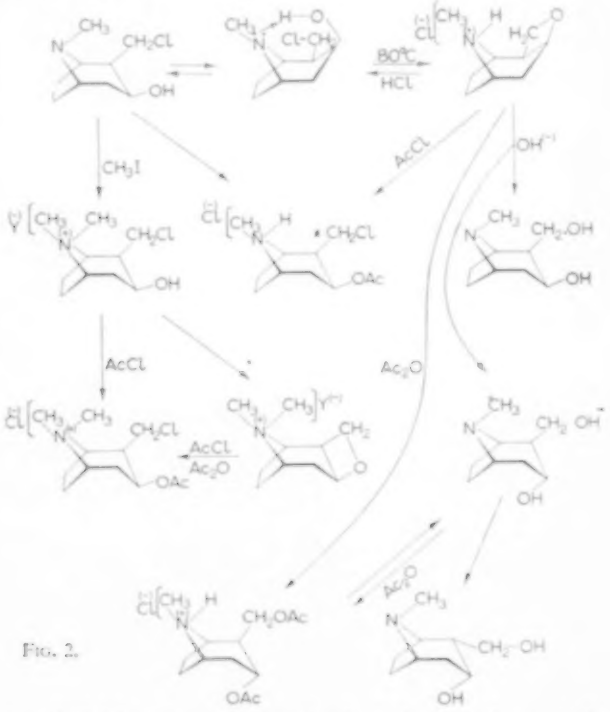

FIG. 2.

2β-Hydroxymethyl-3β-tropanol (ecgoninol) and 2α-hydroxymethyl-3β-tropanol (ψ-ecgoninol) furnished, on oxidation with silver oxide, good yields—the latter rather than the former—of the corresponding carboxylic acids, i.e. ecgonine and ψ-ecgonine.[11]

[8] R. B. Clayton and H. B. Henbest *Chem. and Ind.* 1315 (1953).
[9] E. Hardegger and H. Ott *Helv. Chim. Acta* **38**, 312 (1955).
[10] W. v. E. Doering and T. C. Ashner *J. Amer. Chem. Soc.* **75**, 397 (1953).
[11] M. Hálmos, Ö. Kovács, and G. Fodor *J. Org. Chem.* (In the press).

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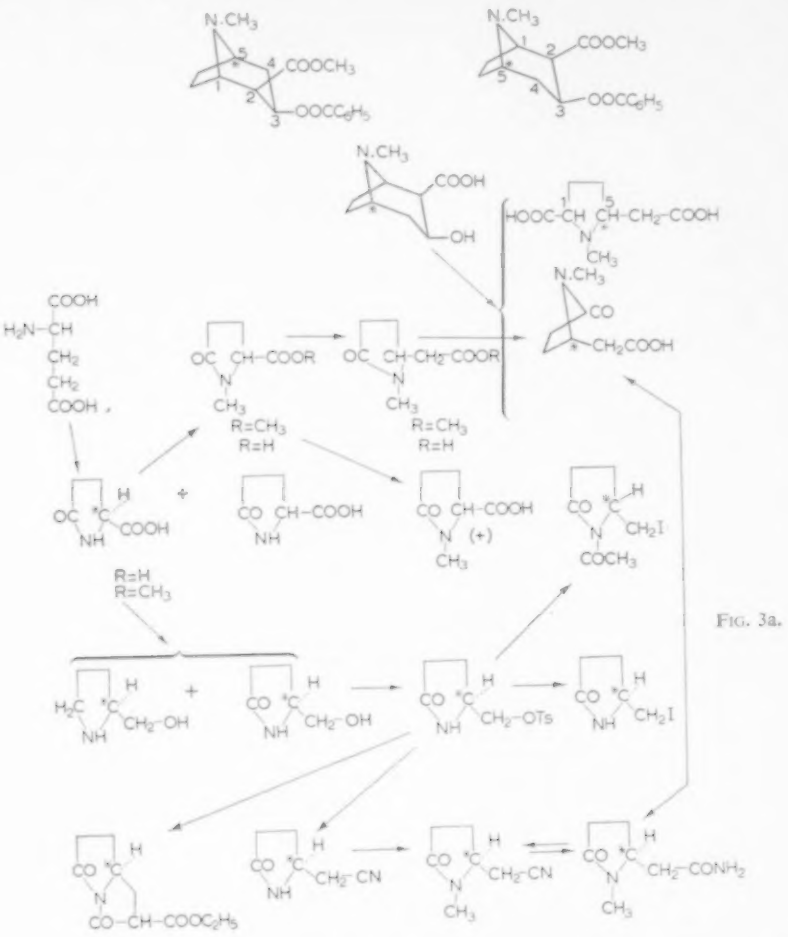

FIG. 3a.

(Fig. 3b). Unfortunately, however, the 3α-hydroxylated derivatives did not undergo this selective oxidation at all, for the 2α·3α-modification has been recovered completely unchanged, while the 2β·3α-derivative has been oxidised partly to a tar in addition to a considerable amount of unchanged diol.

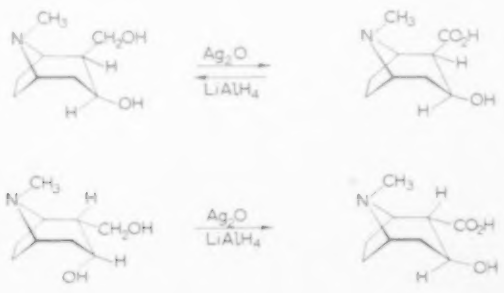

FIG. 3b.

The second method outlined above was rather classical, and in the hands of German and American colleagues gave a positive response to the questions of synthesis.

The "third" racemate prepared according to Willstätter[12] has been benzoylated to the new cocaine.[13] Somewhat later hydrogenation of methyl tropinone-2-carboxylate over Adams platinum catalyst has been described to afford 80% yield of the "third" racemic ecgonine methyl ester.[14] Alkaline hydrolysis furnished a mixture of ecgonines, presumably of the "third" and "fourth" racemates, both of which have been benzoylated into the cocaines. Unfortunately, the physical constants recorded by the two teams show a marked and unaccountable discrepancy. To the "third" racemate the configuration of 2β-methoxycarbonyl-3α-tropanol has been allotted by analogy to ecgonine (epimerisation by alkali during both hydrolysis and quaternisation with methyl iodide)[14] the fourth representing consequently the 2α·3α-modification (Fig. 4).

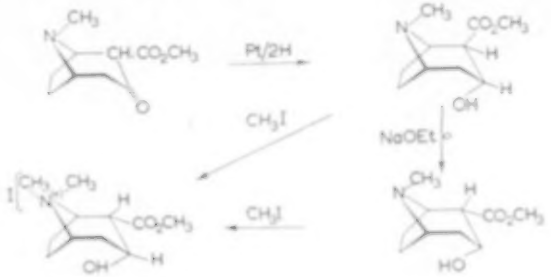

FIG. 4.

(b) *The total synthesis of scopolamine and hyoscine*

Until 1923 the suggested chemical constitution of this alkaloid was accepted,[15] although none of the fourth steric structures could be ascribed to it. During recent years the configuration of (±)3α-tropyloxy-6·7β-epoxy tropane has been verified for scopolamine, based upon modern interpretation of its conversion into oscine,[16,17,18] and into scopinium bromide,[17,18] respectively, to which lent support also its hydrogenolysis[19] into (±)3α·6β-dihydroxy tropane. This latter has been obtained by total synthesis from malic dialdehyde,[20] followed by the resolution[19] of the latter into the alkamine[21] of valeroidine.[22]

Synthesis had been attempted earlier than this recent stereochemical work, but no success was recorded; e.g. epoxy-succinic dialdehyde prepared both by periodic acid oxidation of conduritoxide,[23] and from 2·5-dimethoxy-2·5-(2H)-furan[24] was submitted to Robinson condensation with methyl amine and acetone dicarboxylic

[12] R. Willstätter, O. Wolfes, and O. Mäder *Lieb. Annalen* **434**, 111 (1923).
[13] K. Zeile and W. Schultz *Ber.* **89**, 678 (1956).
[14] St. P. Findlay *J. Org. Chem.* **21**, 711 (1956).
[15] R. Willstätter and E. Berner *Ber.* **56**, 1079 (1923).
[16] G. Fodor *Nature* **170**, 278 (1952).
[17] J. Meinwald *J. Chem. Soc.* 712 (1952).
[18] R. C. Cookson *Chem. and Ind.* 337 (1953).
[19] (a) G. Fodor, Ö. Kovács, and L. Mészáros *Research* **5**, 534 (1952).
(b) G. Fodor and Ö. Kovács *J. Chem. Soc.* 2341 (1953).
[20] A. Stoll, B. Becker, and E. Jucker *Helv. Chim. Acta* **35**, 1263 (1952).
[21] O. Wolfes and O. Hromatka *Merck's Jahresber* **47**, 45 (1934).
[22] G. Barger, F. Martin, and W. F. Mitchell *J. Chem. Soc.* 1820 (1937).
[23] Cl. Schöpf and L. Schmetterling *Angew. Chem.* **64**, 691 (1952).
[24] J. C. Sheehan and B. M. Bloom *J. Amer. Chem. Soc.* **74**, 3825 (1952).

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acid, which gave a tricyclic hydroxy derivative instead of the expected ketone, i.e. scopinone. Thus the use of a building stone containing the preformed epoxide bridge proved unsuitable for this synthesis.

A different line of approach has been suggested by Preobrashenski, who intended to oxidise $\Delta_{6,7}$-tropenol to scopine and teloidine (Fig. 5.) The key intermediate, 6-

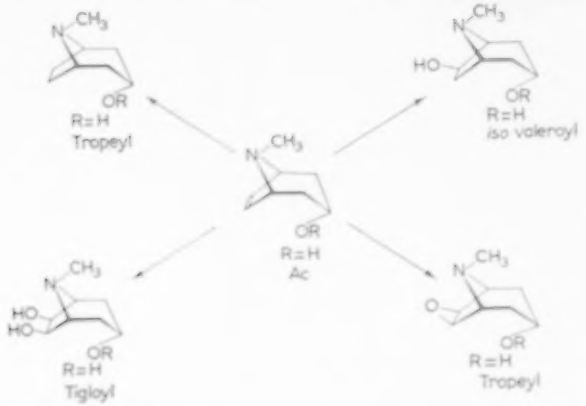

FIG. 5.

tropen-3-one, was described as early as 1945 by the Russian authors; unfortunately, however, its preparation from maleic dialdehyde has never been successful in the hands of other authors.[26] The product seems to have consisted of impure tropan-3-one.[27]

Even if this unsaturated ketone were available there is ample reason to anticipate its easy aromatisation into tropone,[27] the more so since tropanone methiodide gives in an analogous manner dihydrotropone[28] (Fig. 6.)*

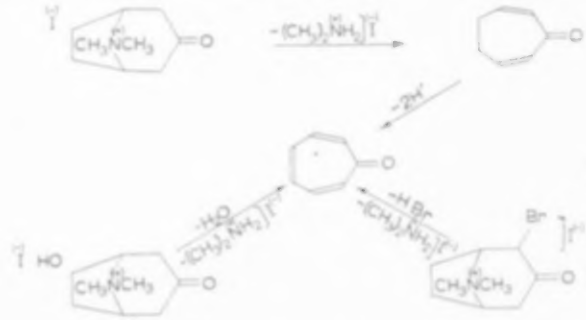

FIG. 6.

To overcome this undesirable intermediate, but adopting tropenol as a key, our team[29] chose a devious way, by selective dehydration, of 3α·6β-tropandiol, i.e. of a

[25] N. A. Preobrashenski, I. A. Rubtzov, T. F. Dankova, and V. P. Pavlov *J. Gen. Chem.*, Moscow **15**, 952 (1945).
[26] J. Kebrle and P. Karrer *Helv. Chim. Acta.* **37**, 484 (1954).
[27] This concept has been suggested by Prof. Cl. Schöpf.
[28] G. Büchi, N. C. Yang, S. L. Emermann, and J. Meinwald *Chem. and Ind.* 1063 (1953); *J. Amer. Soc.* **77**, 4401 (1955); * *Added in proof.* Meanwhile E. E. van Jamelen succeeded in converting 6-hydroxy-tropan-3-one methiodide directly into tropone.
[29] G. Fodor, J. Tóth, I. Koczor, I. Vincze, and P. Dobó The Institute of Organic Chemistry, The University of Szeged, Hungary.

stable tropane derivative with subsequent oxidation of the double bond to the epoxide bridge.

There were four theoretical questions to be considered before commencing experimental work.

(1) Dehydration of tropan-3α·6β-diol to be carried out in a selective manner;

(2) If so, would the unsaturated tropane which forms be not too stained to survive isolation and oxidation?

(3) What could be expected concerning the steric course in oxidising the double bond?

(4) How to avoid competitive oxidation of the nucleophilic nitrogen of tropenol.

To the second question a positive answer has been given as a result of having examined Leybold atomic scale models of 6-tropen-3-ol prepared according to Stuart and Briegleb, since this seemed, unexpectedly, to bear lower strain than the dihydro derivative, tropine.

As to the third problem, the oxidation on the ethylenic bond of trop-6-en-3α-yl acetate was expected to take an *exo*-course, for in analogous bridged bicyclic systems this rule[32] proved of general use.

Selective dehydration of the tropandiol prepared from 2·5-dimethoxy-2·5-dihydro furan according to Clauson-Kaas and his pupil[30] could be performed in two different ways. (1) Action of phosphorus oxychloride led by an S_N2i mechanism to (±)-3α·6α-oxydo tropane, the levorotatory form of which was already described[21] as early as 1934. Ring cleavage of the racemate with acetyl bromide gave rise to a bromotropanyl acetate which, in turn, could be dehydrobrominated by collidine into tropen-yl acetate. The location of the double bond at $C_{6,7}$ and that of the esterified hydroxyl group at C_3 arose from its hydrogenation leading to tropan-3α-yl acetate. Thus ring cleavage has been introduced by an S_N2 attack of bromine upon the C_6-bridgehead of the oxydo group and the acetylated oxygen function remained linked to C_3 (Fig. 6).

The same unsaturated alcohol has been produced by converting 6β-hydroxy-tropan-3-one into its phenyl urethane followed by (1) hydrogenation, acetylation of 3α·6β-dihydroxy tropane 6-phenylurethane, and (3) cleavage of 3α-acetoxy-6β-phenylcarbamyloxy-tropane into 6β-hydroxy tropane-3α-yl acetate. Tosylation and subsequent heating with collidine of the toluene-sulphonic ester yielded trop-6-en-3α-yl acetate again[31] (Fig. 7).

The greatest difficulty was caused by competition of nucleophilic nitrogen in tropenol concerning oxidation with electrophilic reactants, e.g. with organic peracids. Slight excess of monoperphtalic acid gave rise to the *N*-oxide, while with 20 moles subsequent epoxidation has been realised also into acetyl-scopine *N*-oxide which has been identified by its hydrogenolysis into (±)3α-acetoxy-6α-hydroxy tropane.[33] The yields, however, have not been satisfactory; in addition, this second step of oxidation took a month.

The low conversion achieved by monoperphthalic acid has been explained by R. B.

[30] P. Nedenskov and N. Clauson-Kaas *Acta Chem. Scand.* **8**, 2295 (1954).
[31] (a) Fodor and co-workers, lecture, XIVth International Congress of the I.U.P.A.C., Zürich, 21 July 1955; (b) G. Fodor, J. Tóth, I. Koczor, and I. Vincze *Chem. and Ind.* 1260 (1955).
[32] K. Alder and H. A. Dortmann *Ber.* **86**, 1544 (1953).
[33] G. Fodor, J. Tóth, I. Koczor, P. Dobó, and I. Vincze *Chem. and Ind.* 764 (1956).

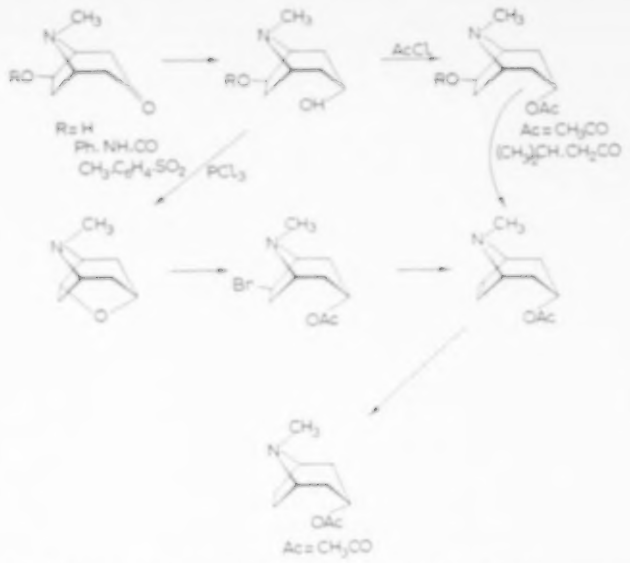

FIG. 7.

Woodward,[34] who postulates a catalytic role of aminoxydes in decomposing peracids according to the following equation:

$$R_3N \rightarrow O + R\text{-}CO_3H = R_3N\text{:} + O_2 + R\text{-}COOH$$

Consequently, blocking of nitrogen before oxidation seemed preferable. Both the hydrochloride and perchlorate of tropenyl acetate, however, withstood any attempt of oxidation[33] indicating a marked decrease in nucleophilic activity of the double bond induced by the *—I* effect of quaternary ammonium nitrogen.

To overcome this difficulty the stronger electrophilic trifluoroperacetic acid[35] has been adopted in place of monoperphtalic acid, allowing it to react upon the trifluoroacetic-acid salt of tropenyl-acetate, which led to acetyl scopine.[33] Identification has been carried out by means of an authentic sample obtained on acetylation of scopine, this latter being prepared by mild hydrolysis from scopolamine, according to Willstätter and Berner.[15]

After having fulfilled the four above-mentioned prerequisites for synthesis, we had as our last task to reconvert scopine into acetyl scopolamine and hyoscine, respectively.

Selective hydrolysis of the acetyl group has been performed under very mild conditions according to the method outlined by Kunz and Hudson,[36] i.e. using N NaOH in acetone.

In tropylation reaction, however, several difficulties arose.

After a series of unsuccessful attempts, acylation of scopine hydrochloride could be realised by using excess acetyltropyl chloride in nitrobenzene at 65°C. Separation of acetyl scopolamine has been achieved by partition chromatography on cellulose powder column,[33,37] followed by selective hydrolysis which led to scopolamine hydrochloride, identical in every respect with the natural alkaloid (Fig. 8). Since the

[34] Personal communication to the author, Zürich, 23 July 1956.
[35] W. D. Emmons and A. S. Pagano *J. Amer. Chem. Soc.* **77**, 89 (1955).
[36] A. Kunz and C. S. Hudson *Ibid.* **48**, 1982 (1926).
[37] G. Fodor, Lecture, Joint Colloquy of the Chemical Institute of the University and of the Organic Chemical Institute of Swiss Federal High School, Zürich, 3 May 1956.

latter was already resolved in 1919 by King[38] into the dextrorotatory form, and later by Preobrashenski[39] into both antipodes, this synthesis may be considered as an equivalent of that of hyoscine.

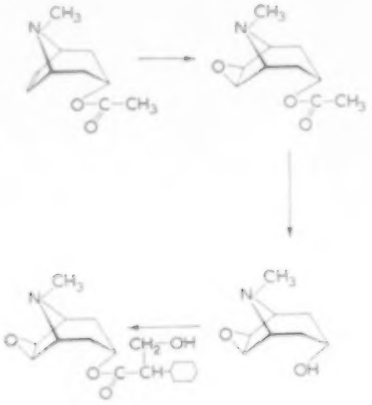

FIG. 8.

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(c) *The total synthesis of valeroidine*

The relative configuration of valeroidine as that of (−)6β-hydroxy-3α-*iso*valeroxy tropane has been established,[19,40,41] while its absolute configuration is still subject to further investigations. The conclusions reached hitherto are supported by the following facts: (1) Hydrogenolysis of scopolamine into the racemic form[19] of the alkamine of valeroidine (so-called valerine) with subsequent resolution into the alkamine, indicated the presence of a 3α-placed hydroxyl, since the rearrangement of scopine into oscine could not take place if this group would have β-location; (2) oxidation of valeroidine gave besides *nor*-valeroidine a compound the analytical data of which pointed to the structure of the cyclic urethane derived of *nor*-valeroidine.[41] This may be considered as evidence for the β position of the unbound hydroxyl group in valeroidine; (3) (±)valerine furnished on the action of ethyl iodoacetate the $\langle N{\cdot}C_6\rangle$ lactone of N_b-carboxymethyl-3α·6β-dihydroxy tropanium iodide,* which provides decisive proof for the β-position of the C_6-hydroxyl group.[40]

Concerning synthesis of the alkaloid, (±)6β-hydroxy tropan-3-one has been resolved[20] and hydrogenated into (+) and (−)3α·6β-tropandiol.[42] Both have been esterified with *iso*valeryl chloride to yield the di-*iso*valeric ester[42] which, unfortunately, could not be hydrolysed selectively into the 3α-acylated derivative. Similarly, direct monoacylation of the diol also failed.[42]

As a branching off of the route to scopolamine[31,33] (Fig. 8) selective acylation of 3α·6β-dihydroxy tropane seemed feasible. First, (±)6β-phenylcarbamyloxy-3β-hydroxy tropane has been converted into the *iso*valeric ester, and this, in turn, cleaved

* For nomenclature of tropanes see G. Fodor and K. Nádor *J. Chem. Soc.* 1952, 721; for that of the configurations of nitrogen in tropanes see G. Fodor, J. Tóth and I. Vincze *Ibid.* (3504) 1955.

[38] A. King *J. Chem. Soc.* **115**, 476 (1919).

[39] M. N. Shchukina, S. S. Okun, D. N. Yurigin, and N. A. Preobrashenski *J. Gen. Chem.* (*URSS*), **10**, 803 (1940).

[40a] J. Tóth, Lecture, Meeting, Union of Hungarian Chemists, Debrecen, 27 September 1953; *Szerves Kémiai Konferencia Debrecen*, cf. **4**, 293 (1953), *Current Chemical Papers* 620 (1954).

[40b] G. Fodor, J. Tóth, and I. Vincze *Helv. Chim. Acta* **37**, 907 (1954).

[41] Wm. Mitchell and E. M. Trautner *J. Chem. Soc.* 1330 (1947).

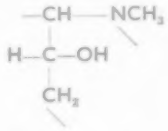
[42] A. Stoll, E. Lindenmann, and E. Jucker *Helv. Chim. Acta* **36**, 1506 (1953).

by thermolysis into (±)valeroidine.[31] The reversible formation of phenylurethanes was earlier studied by Japanese authors,[43] not from the preparative view, but the thermodynamic. This series of reactions could now be adopted to the antipodes arising from the preceding resolution of (±)6-phenyl-carbamyloxy-3α-hydroxy tropane. Consequently, acylation of the levorotatory form and subsequent thermolysis furnished levorotatory 3α·6β-dihydroxy tropane 3-mono-*iso*valeroate, which proved identical[45] in every respect with the natural alkaloid;[44] the dextrorotatory form has also been obtained.

(d) *The absolute configuration of valeroidine*

It has already been intended to correlate (−)3α·6β-dihydroxy tropane and its 3α-*iso*valeric ester, i.e. valeroidine with either D or L-oxo proline[49] by destroying the six-membered ring; this may be by a secondary Beckmann rearrangement of 2·4-dioximoino 6-acetoxy tropan-3-one or of its products of reduction: 6-acetoxy-2·4-dihydroxy-3-amino tropane with periodic acid. These investigations have been commenced by the author's staff as a joint operation with Prof. B. Witkop of the National Institutes of Health, Washington.

However, (−)3α·6β-dihydroxy tropane gave with ethyl iodoacetate the *levorotatory* ester salt, N_b-ethoxy-carbonylmethyl-3α-6β-dihydroxy tropanium iodide, which on heating underwent cyclisation to the *dextrorotatory* ⟨N·C_6⟩ lactone of N_b-carboxymethyl-3α·6β-dihydroxy tropanium iodide. Adopting Hudson's rule valid for γ-lactones[50] it is presumed that the hydroxyl-bearing asymmetric carbon atom concerned in cyclisation belongs to the D series of carbohydrates. Provided this rule can be extended to δ-lactones,[50b] further in considering the group



be depicted by the projection which follows (Fig. 12).

In terms of the recent convention for describing absolute configurations unequivocally, as outlined by Prelog, Cahn, and Ingold,[51] the structure of 3α(R),6β(R)-dihydroxy tropane should be allotted to the alkamine of valeroidine, which, of course, should still be checked by correlation experiments.

(e) *Synthesis of oscine* (*scopoline*)

The author has been informed by Prof. J. C. Sheehan[46] that the Robinson condensation of (±)tartaric dialdehyde followed by reduction led to 3α·6α·7β-trihydroxy

[42] Muhayama Tanaki, Motoki Shimichi, and Hamada Yasuchi *Bull. Chem. Soc. Japan* **26**, 49 (1953).
[44] I. Vincze, J. Tóth, and G. Fodor *J. Chem. Soc.* 1349 (1957).
[45] Author thanks Dr. Wm. F. Mitchell for having submitted an authentic sample of (−)valeroidine hydrobromide.
[46] Verbal communication the 26 July 1955.
[49] G. Fodor, Lecture, Annual Meeting of the Chemical Society in East Germany, 23 October 1954; *Tagungsberichte* 1954, 137–157 Akademie-Verlag, Berlin (1955).
[50] (a) C. S. Hudson *J. Amer. Chem. Soc.* **32**, 338 (1910); (b) P. A. Levene and H. S. Simms *J. Biol. Chem.* **68**, 737 (1926).
[51] R. S. Cahn, C. K. Ingold, and V. Prelog *Exper.* **12**, 81 (1956).

tropane, a derivative which could be cyclised into oscine, i.e. (±)3α·6α-oxydo-7β-hydroxy tropane (Fig. 9). At present the author is unaware of any further publication on this subject.

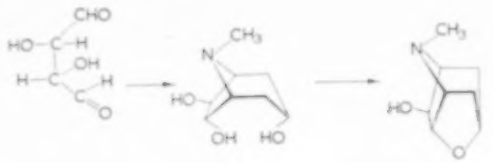
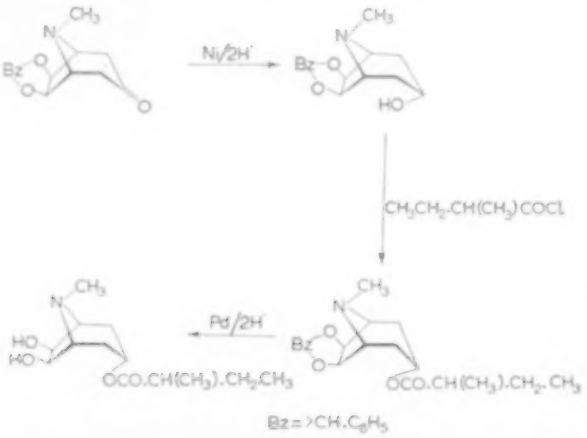


FIG. 9.

(f) *Synthesis of* (2H) *meteloidine*

Teloidinone, i.e. 6β·7β-dihydroxy-tropan-3-one[42] gave a benzylidene derivative[47] which afforded on hydrogenation over Raney-Ni benzylidene teloidine, i.e. 3α·6β·7β-trihydroxy tropane benzylidene ketal. Acylation of the latter with α-methylbutyric anhydride followed by catalytic hydrogenolysis of the benzylidene group over 30% Pd-charcoal furnished dihydro-meteloidine (Fig. 10), identical in every respect with



Bz = >CH.C_6H_5

FIG. 10.

the product which forms by saturation of the double bond in the natural alkaloid.[47] Synthesis of the genuine alkaloid is now in progress.[46]

In addition, a contribution to the stereochemistry of teloidine and ψ-teloidine by Heusner[48] stands on its own merits. Teloidinone acetonide has been hydrogenated selectively into teloidine acetonide and ψ-teloidine acetonide. The latter gave, after v. Braun-degradation, ψ-*nor*-teloidine acetonide, which, in turn, was condensed with *p*-nitro-benzaldehyde into a *meta*-oxazine derivative (Fig. 11), while *nor*-teloidine 3-acetate with the same aldehyde giving an 1·3-oxazolidine, afforded additional evidence in favour of the structure of 3α·6β·7β-trihydroxy tropane for teloidine[41] and of that of 3β·6β·7β-trihydroxy tropane for ψ-teloidine.

[47] J. C. Sheehan and E. R. Bissell *J. Org. Chem.* **19**, 270 (1954).
[48] A. Heusner *Z. Naturforsch.* **9b**, 683 (1954).

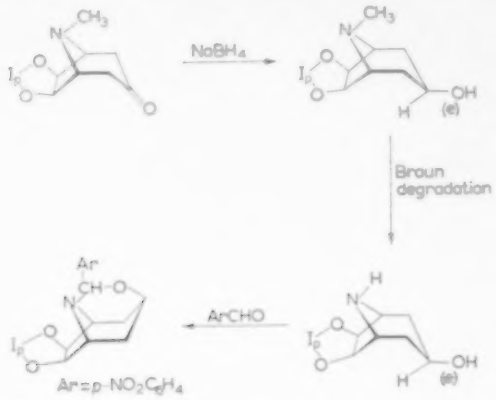


FIG. 11.

2. DETERMINATION OF THE CONFIGURATION OF THE NITROGEN ATOM IN SOME TERTIARY AMINES AND QUATERNARY AMMONIUM SALTS OF THE TROPANE SERIES

A number of preceding papers[52,40,31a,53,54,55] and a review[3,34] dealt with our observations concerning stereospecific routes leading to tropanium salts of definite configurations and with the interpretation[4,53] of this phenomenon. This work, initially done with "direct" and "reverse" quaternisation of tropine and ψ-tropine[52,53] involving direct quaternisation of 3α-6β-dihydroxy tropane, scopolamine, and oscine[41] by means of ethyl iodoacetate into the lactones of the corresponding N-acetic acids, has been extended recently to reverse quaternisation of the latter[53] and to optically active derivatives of the ecgonine[54] and dihydroxy tropane series.[56] These results achieved with some tropane derivatives were treated in detail in a review which appeared last year in *Bulletin de la Société Chimique de France*[57] in terms of the possibility to determine for the first time configurations of asymmetric and of pseudo-asymmetric nitrogen atoms. I intend, therefore, to give but a brief summary of the findings and considerations outlined in this latter contribution which more recent results should help to complete.

(a) (±)3α·6β-dihydroxy tropane gave, on v. Braun degradation, (±)*nor*-3α·6β-dihydroxy tropane, which has been alkylated by means of ethyl iodoacetate to *N*-ethoxycarbonylmethyl-*nor*-3α·6β-dihydroxy tropane.[53] The latter gave, when hydrolysed by hydrochloric acid, the hydrochloride of (±)*nor*-3α·6β-dihydroxy tropane N-acetic acid, but no trace of its lactone salt. Accordingly, the steric conditions of this compound are inadequate to allow ring closure, hence one can deduce the configuration of N_a-carboxymethyl-3α·6β-dihydroxy-*nor*-tropanium chloride for this compound. Quaternisation of the tertiary amine base with methyl iodide gave rise to the tropanium ester salt which could not be cyclised to a lactone after being converted into the betaine and subsequent treatment of the latter with hydrochloric acid. The N-acetic

[52] G. Fodor, Lecture, Meeting of the Union of Hungarian Chemists, Szeged, 20 September 1952.
[53a] G. Fodor, K. Koczka, and J. Lestyán *Magy. Kém. Foly.* **59**, 242 (1953); [b] G. Fodor, J. Tóth, and I. Vincze *J. Chem. Soc.* 3504 (1955).
[54] Ö. Kovács, G. Fodor, and M. Halmos *Ibid.* 873 (1956).
[55] G. Fodor, K. Koczka, and J. Lestyán *Ibid.* 1411 (1956).
[56] G. Fodor, I. Vincze, and J. Tóth To be published in *J. Chem. Soc.*
[57] G. Fodor Lecture Soc. Chim. France, Paris, 27 April 1956; *Bull. Soc. Chim.* 1032 (1956).

acid which formed is represented thence by the structure of (±)N_a-carboxymethyl-3α·6β-dihydroxy tropanium chloride,[53] while the lactone of its epimer, i.e. of (±)-N_b-carboxymethyl-3α·6β-dihydroxy-tropanium iodide arose earlier[40] from a direct action of ethyl iodoacetate upon (±)3α·6β-dihydroxy tropane. The same series of reactions have been carried out with derivatives of oscine and *nor*-oscine,[53] although the results showed marked discrepancy. (Compare Figs. 12 and 13.)

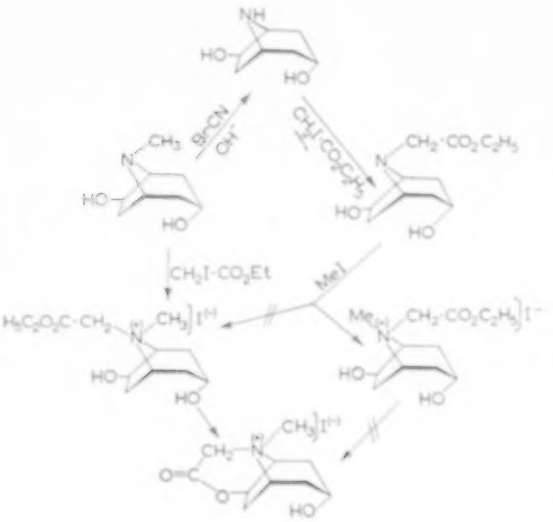


FIG. 12.

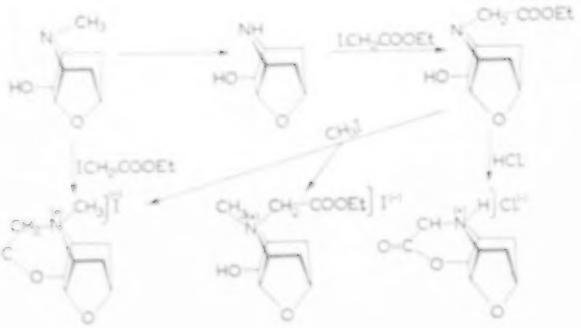


FIG. 13.

(b) (±)Oscine with ethyl iodoacetate gave rise to the lactone of N_b-carboxymethyl-3α·6-oxydo-7β-hydroxy tropane,[40] while *nor*-oscine furnished *N*-ethoxycarbonylmethyl-*nor*-oscine. This latter has been submitted to acid hydrolysis, furnishing a lactone to which the configuration of that of (±)N_b-carboxymethyl-3α·6α-oxydo-7β-hydroxy-*nor*-tropanium chloride has been allotted.[53b] The ester of the foregoing tertiary base afforded with methyl iodide a mixture from which the lactone of N_b-carboxymethyl-3α·6α-oxydo-7β-hydroxy-tropanium iodide and an ester salt could be isolated. The last did not undergo cyclisation even after being converted into

the betaine and heated with hydrochloric acid; thus the structure of N_a-carboxymethyl-3α·6α-oxydo-7β-hydroxy-tropanium chloride has been ascribed to it.[53b] All the compounds in play have therefore definite and known relative configurations, including their nitrogen atoms (Fig. 13).

As to the reason of this striking influence of the 3·6-placed oxygen bridge upon stability of configurations at the tertiary amine stage, which is depicted by the tendency of the oscine derivatives to give both *N*-epimeric ammonium salts possible—the marked decrease of Pitzer-strain[58] in the five-membered ring of oscine as compared with that prevailing in 3α·6β-tropandiol is considered responsible. More explicitly, the smaller deviation from coplanarity the smaller the Pitzer effect which may expel the methyl group on nitrogen to assume with greater probability the axial, i.e. N_a position, hence entrance of the quaternising group in either N_a or N_b position seems equally feasible.[53b,57]

(c) A further series of experiences has been collected with derivatives of ecgoninol, i.e. (−)2β-hydroxymethyl-3β-tropanol.[54] "Direct" quaternisation of its diacetate with ethyl iodoacetate gave rise to an ester salt, while *N*-ethoxycarbonylmethyl-*nor*-ecgoninol could be converted on action of methyl iodide into the lactone of (−)-N_a-carboxymethyl-2β-hydroxymethyl 3β-hydroxy-tropanium iodide, conceivably the ⟨2¹·*N*⟩ lactone, for this may be formed even in the chair form of the six-membered ring. The epimeric ester salts, carboxylic acids, and betaines involving their (α_D) values have been described in detail.[54]

This is the first time that the absolute configuration of a quaternary ammonium salt having an asymmetric nitrogen could be established, though this model contains a number of asymmetric carbon atoms also.

Provided we are authorised to extend the principles of Ingold, Cahn, and Prelog[51] to designate absolute configurations of tetrahedral nitrogen, the following notations should be allowed: since (−)cocaine has been proved as 2β(R)-methoxycarbonyl-3β-(S)-benzoxy tropane and (−)ecgoninol as 2β(S)-hydroxymethyl-3β(S)-benzoxy-tropane, the compound of direct quaternisation is thus represented by N_b(S)-carboxymethyl-2β(S)-hydroxymethyl-3β(S)-hydroxy tropanium chloride, while its *N*-epimer is N_a(R)-carboxymethyl-2β(S)-hydroxymethyl-3β(S)-hydroxy tropanium chloride (Fig. 14).

(d) The next series of investigations, carried on with optically active 3α·6β-dihydroxy tropane and oscine, may provide information regarding the contribution of the

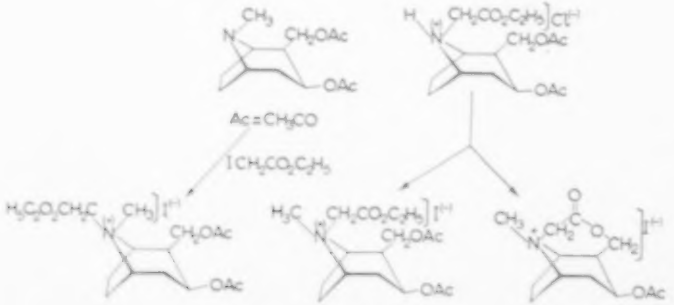


Fig. 14.

[58] Ch. W. Beckett, K. S. Pitzer, and R. Spitzer *J. Amer. Chem. Soc.* **69**, 2488 (1947).

steric position of substituents on asymmetric nitrogen to the whole asymmetry of the molecule.[56]

(e) Furthermore, X-ray determinations of the absolute configurations of tropine ethochloride and *N*-ethyl-*nor*-tropine methochloride are still in progress at the University of Amsterdam.[59]

3. ENOL ISOMERISM AND RING OPENING IN THE TROPINES

(a) A tropine derivative, i.e. α-hydroxy-methylene-phenylacetyl tropeine, served as an adequate substrate to study geometrical isomerism around the enolic double bond.[60] The *cis*-modification (concerning carbonyl and hydroxyl) proved by infra-red spectra to be stabilised by hydrogen bonding, while the *trans* form seems to be an enol betaine. Indeed the oxo form seems to be negligible, for no easy stereomutation has been recorded (Fig. 15).

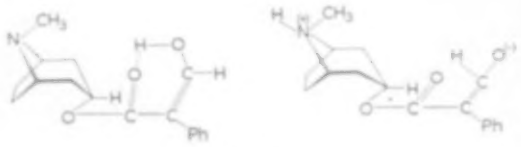


FIG. 15.

(b) Evidence has been presented for the bromination of tropinone to give rise to 2β-bromo tropinone (hydrobromide, m.p. 192°).[61] Sodium borohydride reduction of this latter furnished a bromohydrine (m.p. 125·5°), hydrogenolysis of which over Pd—C leads to 3β-tropanol, while alkaline treatment yielded tropinone. This confirmatory evidence points to the β-placed hydroxyl as being *cis* to bromine. An interesting reversible ring opening has been presented with 3β-tropanol methohydroxide into 6-dimethyl-amino-*cyclo*hept-2-en-1-ol, the dibromide of which has been reconverted by sodium hydrogen carbonate into the methobromide of the same bromo-alcohol.[61] Hence, the eliminated bromine must have been *trans* to the $N(Me)_2$ group, so the preserved one is obviously *cis*-placed to the *N*-methyl bridge in the 2-bromo-tropanol concerned[61] (Fig. 16).

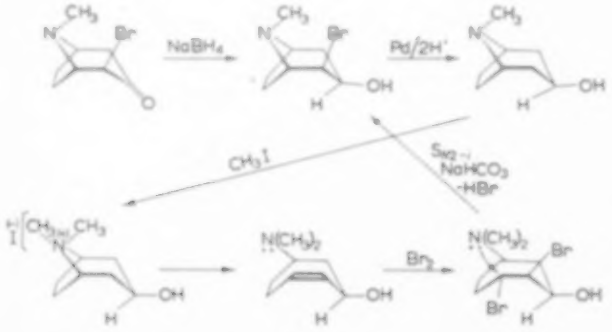


FIG. 16.

[58] Author thanks Prof. Dr. Caroline McGillavry for having paid attention to this subject.
[60] C. A. Friedmann and J. M. Z. Gladych *J. Chem. Soc.* 873 (1956).
[61] A. Nickon *J. Amer. Chem. Soc.* 77, 4094 (1955).

4. INVESTIGATIONS AND CONSIDERATIONS CONCERNING THE STRUCTURE OF DIOSCORINE

A tentative formula of the γ-lactone of 2-(α)-*iso*propylidene-carboxymethyl-3-hydroxy tropane has so far been suggested to dioscorine based merely upon positive Legal test, indicating the presence of an α·β-olefinic lactone grouping[62] as well as an exhaustive methylation[62] described in detail in Manske-Holmes' monograph, *The Alkaloids*, Vol. I. The isolation of the alkaloid from different sources;[64] furthermore, its degradation has been recently[64] reinvestigated, adopting modern experimental methods, *inter alia* techniques of infra-red spectroscopy.[65] The base $C_{13}H_{21}N$ obtained first by Hofmann degradation broke down when heated with palladised charcoal into trimethylamine, an unidentified base, and *iso*butyl-benzene, or β·β-dimethylstyrene, depending on the activity of catalyst. Another item of exhaustive methylation of this base gave a hydrocarbon, $C_{11}H_{14}$, infra-red spectroscopic data of which support the structure of *iso*butenyl *cyclo*heptatriene, containing a $\begin{matrix} R_1 \\ R_2 \end{matrix}\!\!>\!C{=}CH_2$ linkage. Hydrogenation of this compound yields, however, a hydrocarbon $C_{11}H_{22}$, infra-red data which are very similar to those but not identical with the curve of *i*-butyl-*c*-heptane, obtained on synthesis[65] from 4-*i*-butyl-*cyclo*hexanone by ring enlargement with diazomethane, followed by Kishner-Wolf reduction of *i*-butyl *cyclo*heptanone.

On the other hand, two of the structural isomers (1 : 3, 1 : 4) possible of *N*·*N*-dimethyl-*i*-butyl-*c*-heptylamine have been synthesised. The infra-red curves were very close to those of the saturated Hofmann base $C_{12}H_{27}N$, none of them proved, however, identical with that of the base from dioscorine. Configurations have not been taken into consideration, so these data are not sufficiently conclusive. Nevertheless, a new tentative formula has been suggested[65] which takes account for the formation of a $C{=}CH_2$ group on decarboxylation of the hydroxy-acid from dioscorine, i.e. that of the ε-lactone of a tropine derivative with a β-methyl-α·β-butenoic acid side-chain in position 2.[65] Although these new investigations may seem satisfactory in explaining the structural problem, in the author's opinion, they need synthetic confirmation. As to stereochemical predictions, the mydriatic effect of dioscorine supports strongly the presence of a 3α-placed hydroxyl group. Furthermore, Stuart-Briegleb models allow the existence of both *cis* and *trans* anellation of the seven-membered unsaturated lactone ring to the piperidine ring of tropane (Figs. 17 and 18).

5. SOME RECENT CONTRIBUTIONS TO THE PROBLEM OF BIOGENESIS OF SCOPOLAMINE AND HYOSCYAMINE

In preceding reviews[3,4] this question has been discussed both in terms of syntheses under so-called physiological conditions[66] and considering some feeding experiments on living Datura plants, controlled by the isotopic tracer techniques.[67] Establishing of the configurations of all the natural tropane bases valeroidine, scopolamine, and meteloidine bearing oxygen function(s) at the ethylene bridge,[40,41] which proved to be *cis*, i.e. β-placed to the nitrogen allowed the assumption of a common precursor for all

[62] K. Gorter *Rec. Trav. Chim.* **30**, 161 (1911).
[63] K. Gorter *Ann. Jardin Biol. Buit.* (11) Suppl. **3**, 385 (1910).
[64] A. Pinder *J. Chem. Soc.* 2236 (1952); 1825 (1953).
[65] A. Pinder *J. Chem. Soc.* 1577 (1956).
[66] Cl. Schöpf and his school *Angew Chem.* **64**, 591 (1952).
[67] L. Marion *et al.* *Canad J. Chem.* **29**, 964 (1951).

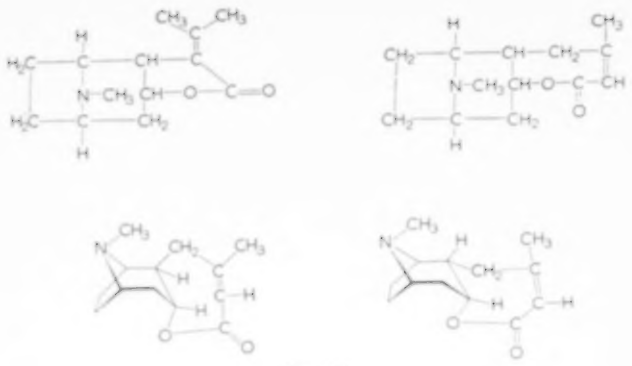


FIG. 17.

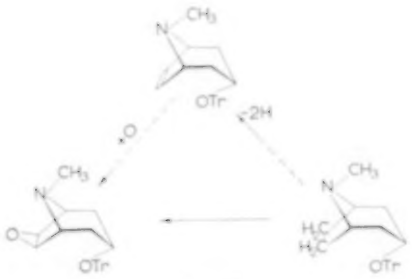


FIG. 18.

these alkaloids. Δ_6-Tropen-3-ol was propounded as early as 1944 as the most probable compound of this type.[68,69] Stereospecific *exo*-additions[32] of different addenda to it may afford the above-mentioned tropeines. Unfortunately, however, until 1955 this key intermediate was not available. Recent synthesis of scopolamine[31b, 33] by way of tropenol makes it possible in the near future to perform feeding experiments with this unsaturated alcohol.

However, we were discouraged by the fact that recent feeding experiments on *Datura strammonium* with α-^{14}C-labelled ornithine led to C_1-radioactive hyoscyamine (atropine) but radio-inactive hyoscine (scopolamine).

Surprisingly, Romeike succeeded in carrying out feeding experiments with young *Datura ferox* plant, itself unable to produce hyoscine, which proved to convert[71] fed hyoscyamine into hyoscine. This latter has been identified by paper chromatography and also by its crystalline picrate.[72]

Hence, the central role of tropenol in biosynthesis of tropanols might not be discarded, but requires still many systematic feeding experiments with tropenol derivatives. These joint efforts are already being carried out in Gatersleben[73] and in the author's laboratory.[29]

[68] B. T. Cromwell *Biochem. J.* **37,** 717–722 (1944).
[69] N. A. Preobrashenskii and E. I. Genkin *Chemistry of Organic Pharmaceutical Products* (in Russian) p. 181, Gozchimizdat, Moscow (1953).
[70] E. Leete, L. Marion, and I. D. Spenser *Nature* **174,** 650 (1954).
[71] A. Romeike *Angew. Chem.* **68,** 124 (1956).
[72] A. Romeike *Flora (Jena)* **143,** 67 (1956).
[73] Two lectures, delivered at the Symposium on Biochemistry and Physiology of Alkaloids by A. Romeike and G. Fodor resp. Quedlinburg, 8–12 October 1956.

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Tetrahedron, 1957, Vol. 1, pp. 103–118. Pergamon Press Ltd., London

STUDIES IN THE TRIAZINE SERIES INCLUDING A NEW SYNTHESIS OF 1:2:4-TRIAZINES

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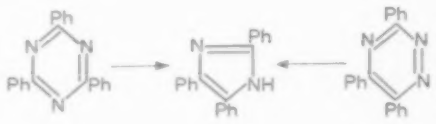
(*Received* 11 *February* 1957)

Abstract—The mono-aroylhydrazones of benzil are cyclised by ammonium acetate in hot acetic acid to tri-substituted-1:2:4-triazines. The yield is favourable and it is not necessary, or even advantageous, to isolate the presumed intermediates. The new synthesis has been applied to a sufficient range of examples to establish its status as a general method. In the case of phenanthraquinone the reaction took a more complex course and probably involved two molecules of the diketone.

A rational synthesis of kyaphenine (2:4:6-triphenyl-1:3:5-triazine) has been effected by reaction of 2-chloro-4:6-diphenyl-1:3:5-triazine with phenylmagnesium bromide and a similar method served to synthesise 5:6-diphenyl-3-*p*-tolyl-1:2:4-triazine also made from benzil and *p*-toluylhydrazide. Both kyaphenine and its isomeride in the *asymm*-triazine series afford lophine on reduction, and the mechanism of the long-known former reaction (Radziszewski) is discussed.

The reduction of kyaphenine (I), by means of zinc and acetic acid, with formation of lophine[1] (II) appeared noteworthy from the point of view of reaction mechanism, and consideration of the problem prompted the present investigation. *Triphenyl*-1:2:4-*triazine* (III) was not known and, as the facile transformation of this substance to lophine could be predicted, independent step-wise syntheses of the isomeric triphenyl-triazines, I and III, were sought.



I II III

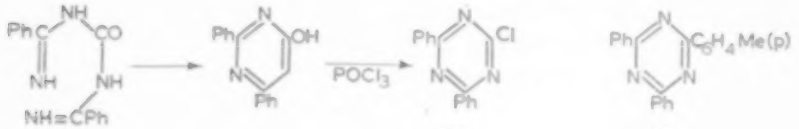
None of the known methods of synthesis of kyaphenine and analogous substances served to establish the structural formulae, e.g. both I and III could theoretically be obtained by trimerisation of benzonitrile. It transpired that the expression I for kyaphenine could be confirmed by unequivocal synthesis. The isomeride (III), obtained as described below, has very different properties, but, as anticipated, also gives a good yield of lophine on reduction with zinc and acetic acid. Most of the known kyaphenine syntheses can be assumed to proceed via benzonitrile, possibly in an activated form; examples are the reaction of benzene with cyanogen bromide in the presence of aluminium chloride[2] and the decomposition of benzimino methyl ether on keeping.[3]

The conversion of cyanuric chloride (trichloro-*symm*-triazine) to kyaphenine was

[1] B. Radziszewski *Ber.* **15**, 1493 (1882).
[2] R. Scholl and W. Nörr *Ber.* **33**, 1052 (1900).
[3] T. B. Johnson and L. W. Bass *J. Amer. Chem. Soc.* **54**, 1341 (1922).

claimed by Klason,[4] who treated the substance with bromobenzene and sodium in an ethereal medium. The main product was diphenylchloro-*symm*-triazine (IV). Kraft[5] repeated the experiment with some modifications and stated that kyaphenine, m.p. 233°, could be isolated. However, Cook and Jones[6] have further examined the reaction but did not obtain kyaphenine.

The present authors find that 6-chloro-2:4-diphenyl-1:3:5-triazine (IV), m.p. 141–142°, is converted into kyaphenine in good yield by reaction with phenylmagnesium bromide. Similarly diphenyl-*p*-tolyl-*symm*-triazine (V) was obtained by the use of *p*-tolylmagnesium bromide.

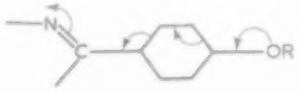


IV V

The method of preparation[7] of (IV) through the corresponding hydroxytriazine, itself made from benzamidine and phosgene,[8] appears to guarantee its *symm*-triazine structure.

A very convenient method for the trimerisation of benzonitrile and many of its derivatives is to treat them with chlorsulphonic acid in chloroform solution. This was first used[9] by Brown and Robinson in the case of piperononitrile, but, on account of its strong halochromic properties, the product was thought to be a dimeride, namely a dimethylenedioxyanthraquinonedi-imide. Unfortunately, this was fully confirmed by Keffler[10] by the determination of the M. W. (cryoscopic in thymol) of three substances. These all gave close to two-thirds of the correct figures, and a similar error was made later in the series of the condensation products of formaldehyde and veratrole. The only explanation of this appears to be a miscalculation of the constant for thymol. The trimeric character of the substances was established by Wilson.[11] During the present investigation it was noted that a moderately satisfactory result was obtained by the micro-Rast method (cryoscopic in camphor) of determination of the M. W. in the case of these sparingly soluble kyaphenines.

The halochromy of the *p*-alkyloxyphenyltriazines is characteristic and suggests an electron displacement of the annexed type.



There is, however, some contribution from each of the aryl groups, and how these are linked through the central nucleus can only be conjectured. The mechanism of the

[4] P. Klason *J. Prakt. Chem.* (2), **36**, 82 (1887).
[5] F. Krafft *Ber.* **22**, 1759 (1889).
[6] A. H. Cook and D. G. Jones *J. Chem. Soc.* 279 (1941).
[7] J. Ephraim *Ber.* **26**, 2226 (1893); Cf. *Org. Synth. Coll.* **1**, 6 (1946).
[8] A. Pinner *Ber.* **23**, 163, 2920, (1890).
[9] J. G. McG. Brown and R. Robinson *J. Chem. Soc.* **111**, 952 (1917).
[10] L. P. G. Keffler *J. Chem. Soc.* **119**, 1476 (1921).
[11] C. V. Wilson *J. Amer. Chem. Soc.* **70**, 1901 (1948).

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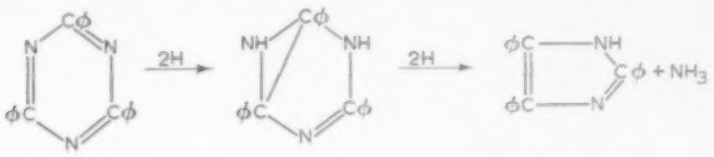
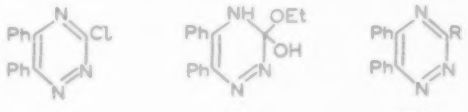
reduction of kyaphenine to lophine appears to the authors to be analogous to the formation of a pinacol from a ketone (cf. ref. 14):



It is very interesting that the process can be reversed[12] by reaction of lophine with iodine in gently boiling liquid ammonia with production of kyaphenine.

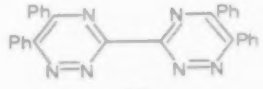
The 1:2:4-*triazine series.* It is curious how little attention has been paid to this group insofar as the analogues of alkyl or aryl *symm*-triazines are concerned. The hydroxy-, amino-, and thiol *asymm*-triazines have, however, been known for many years. Condensation of benzil and semicarbazide makes 3-hydroxy-5:6-diphenyl-1:2:4-triazine readily accessible.[13] We have examined the corresponding chloride (VI) which is obtained by the action of phosphoryl chloride on the hydroxy-compound. Unusually, it has a higher m.p. than its *symm*-analogue (IV). The halochromy of VI is more pronounced than that of IV; red and yellow solutions, respectively, in sulphuric acid. Furthermore, the halogen of VI is much more labile than that of IV. In boiling methanol or ethanol, hydrogen chloride is liberated and the products are found to be hydrates of the expected alkyloxydiphenyl-*asymm*-triazines. The product from ethanol has m.p. 220°, with decomposition to ethanol and 3-hydroxy-5:6-diphenyl-1:2:4-triazine. This substance can hardly be a hydrate or ethanolate, and may have the structure VII.



VI VII VIII

With hydrazine, VI affords a hydrazino-derivative (VIII, R = NH·NH$_2$) which is oxidised by cupric salts to 5:6-diphenyl-1:2:4-triazine (VIII, R = H). The halochromy is throughout stronger in the *asymm* than in the *symm* series. This diphenyl-*asymm*-triazine gives a crimson solution in sulphuric acid. With phenylhydrazine in pyridine solution, VI affords the phenylhydrazino-derivative (VIII, R = NH·NHPh), which was oxidised by ferric chloride to a dark-coloured material (presumably VIII, R = N=NPh).

The pyrolysis of this substance did not afford the expected triphenyl-*asymm*-triazine, but a compound which is probably di-(5:6-diphenyltriazinyl-3) (IX).



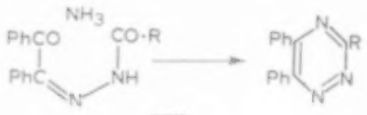
IX

The reaction between chloro-diphenyl-*asymm*-triazine (VI) and phenylmagnesium

[12] H. H. Strain *J. Amer. Chem. Soc.* **49**, 1564 (1927).
[13] H. Biltz *Annalen* **339**, 279 (1905).

bromide also gave an unanticipated result, and should be repeated. Using *p*-tolylmagnesium bromide, however, the diphenyl-*p*-tolyl-*asymm*-triazine (VIII, R = ·$C_6H_4Me(p)$) was isolated. This was identical with a specimen prepared by the method now to be described.

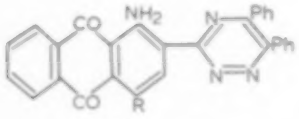
A new synthesis of triaryl-asymm-*triazines.* A preliminary account of this method has been given.[14] Benzil aroylhydrazones are cyclised by ammonium acetate in hot acetic acid solution.



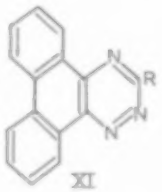
VIII

Since the mono-aroylhydrazones are not in general obtained in high yield from the condensation of benzil and an acid hydrazide, this intermediate stage was not usually isolated. It may be presumed that the *bis*-aroylhydrazone formed is not affected by the reagent in any important side-reaction, but may be a source of the mono-aroylhydrazone as the result of a hydrolytic equilibrium. Hence the generators, that is, α-diketone, acid hydrazide, and ammonium acetate, are mixed in acetic acid and the solution heated. In some cases the product separated from the hot liquid. There is every reason to suppose that the reaction is general for α-diketones, but it did not succeed with phenanthraquinone, at any rate under the usual conditions.

The aroylhydrazones used were those appropriate to introduce the groups, *phenyl* (III), p-*tolyl*, m-*nitrophenyl*, p-*nitrophenyl*, p-*chlorophenyl*, p-*hydroxyphenyl*, p-*aminophenyl*, m-*methoxyphenyl*, 2:4-*dimethoxyphenyl*, 3:4-*dimethoxyphenyl*, 3:4-*methylenedioxyphenyl*, 3:4:5-*trimethoxyphenyl*, α-*furyl*, 1-*amino*-2-*anthraquinonyl*, (X, R = H), and 1:4-*diamino*-2-*anthraquinonyl* (X, R = NH_2) as the group R in the structure VIII.



X



XI

Phenanthraquinone benzoylhydrazone is converted into 1-phenanthrol by boiling aqueous potassium hydroxide. The yield (50%) and convenience of this method constitute considerable improvements on known procedures. The reaction is evidently of Wolff-Kishner-Staudinger type, but when the monosemicarbazone (improved method) was substituted for the benzoylhydrazone cyclisation to 3-hydroxy-5:6-phenthratriazine, (XI, R = OH) occurred. This is a much more convenient process than those previously reported. In fact, we were unable to obtain the substance by De's method;[15] the semicarbazone was recovered unchanged. Our product was identical with a specimen made by the earlier method of Schmidt.[16] Some results incidental to the research are recorded.

[14] P. V. Laakso and R. Robinson *Festschrift Karrer* p. 38 Zürich (1948).
[15] S. C. De *J. Indian Chem. Soc.* **7**, 361 (1930).
[16] J. Schmidt, O. Schairer, and E. Glatz *Ber.* **44**, 276 (1911).

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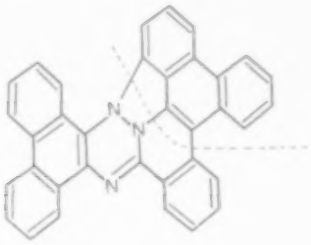
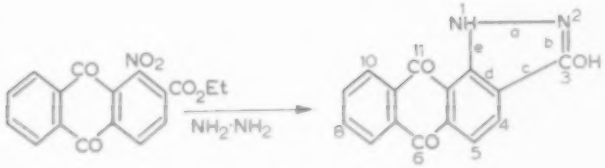
The crystalline, yellow substance obtained from phenanthraquinone benzoylhydrazone and ammonium acetate in boiling acetic acid is apparently $C_{23\text{ or }24}H_{12\text{ or }14}N_2$ on the N_2 basis. As $C_{14}H_8O_2 + C_7H_6O_2 + C_2H_4O_2 + 2NH_3 - 6H_2O = C_{23}H_{12}N_2$, the latter formula (Theory: C, 87·3; H, 3·8; H, 8·9%) may be preferred on analytical grounds. It is, however, hardly possible to construct a plausible formula with so few hydrogen atoms and $C_{23}H_{14}N_2$ (C, 86·8; H, 4·4; N, 8·8%) could be a phenylmethylphenanthrazine with an additional ring, or an isomeric phenanthriminazole derivative.

As this analysis leads to dubious conclusions, N_3 formulae may be considered. The best is $C_{35}H_{19}N_3$ (C, 87·3; H, 4·0; N, 8·7%), and this is $2C_{14}H_8O_2 + C_7H_8ON_2 + NH_3 + 2H - 5H_2O$. This, in our judgement, is the probably correct interpretation. A feasible structure is annexed:



Inspection of this suggestion shows that $C_{35}H_{17}N_3$ can be excluded on structural grounds; $C_{35}H_{21}N_3$ allows one of the rings to be broken (+ 2H) but the analytical results become unsatisfactory.

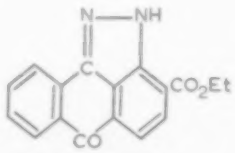
Ethyl 1-nitroanthraquinone-2-carboxylate was converted by hydrazine in hot pyridine into 3-hydroxy-6:11-diketo-1-anthra-(1:2-*d*)-pyrazole (XII) instead of the acid hydrazide.



XII

The enolic form is favoured on account of the ready solubility of the substance in cold aqueous sodium hydroxide.

A second product of the reaction was ethylpyrazole-anthrone-2-carboxylate (XIII), identified by hydrolysis to the corresponding acid which was already known.[17]



XIII

[17] D.R.P. 575,680; *Frdl.* **17**, 1273 (1930).

These two substances (XII and XIII) were also obtained by the action of hydrazine on 1-nitro-anthraquinone-2-carboxylic acid chloride obtained by refluxing the acid with thionyl chloride. This is an improvement on methods previously described.[16]

In order to avoid the complication introduced by the lability of the 1-nitro group in the anthraquinone series, the requisite hydrazides were prepared from corresponding 1-amino-2-carboxylic acids and eventually some 1:2:4-triazines of this group were obtained.

EXPERIMENTAL

Kyaphenine (I). (A) Benzenylbenzamidine[19] (1·0 g, m.p. 77–78°) was heated during 12 hours in a closed vessel with benzaldehyde (0·6 g) on the steam-bath and then at 150° under reduced pressure. The kyaphenine produced (0·2 g) was crystallised from toluene, m.p. 232–33°, alone or mixed with an authentic specimen. (B) 2-Chloro-4:6-diphenyl-1:3:5-triazine was prepared according to the known procedures,[7,8] m.p. 141–42°.

A solution of phenylmagnesium bromide (from 1·1 c.c. of bromobenzene and 0·25 g of magnesium) in ether (10 c.c.) was added to one of the chlorotriphenyl-*symm*-triazine (1·0 g) in benzene (10 c.c.). After refluxing on a steam-bath for 12 hours, the product (0·7 g) was isolated and crystallised from toluene; m.p. 232–233°, alone or mixed with an authentic specimen.

A similar reaction using 2·0 g of *p*-bromotoluene instead of the bromobenzene afforded 2:4-*diphenyl*-6-*p*-*tolyl*-1:3:5-*triazine* (V) which crystallised from toluene in colourless needles, m.p. 199–200° (Found: C, 81·4; H, 5·3; N, 12·3. $C_{22}H_{17}N_3$ requires C, 81·9; H, 5·3; N, 13·0%). It dissolved in sulphuric acid to a yellow solution. It is doubtful whether the substance was previously obtained in a pure state by the co-polymerisation of benzonitrile and *p*-tolunitrile,[20] since the m.p. 176–178° was assigned to the product.

Tri-methylenedioxyphenyl-symm-*triazine*.[9,10,11] The M.W. by Rast's method in camphor was found to be 461, calc. 441. The halochromy of substituted kyaphenines is intensified by alkyloxy groups. In sulphuric acid the colorations are: triphenyl, yellow; tri-*p*-methoxy phenyl[21] and tri-*p*-ethoxyphenyl,[22] deeper yellow to orange-yellow; tri-methylenedioxyphenyl and tri-3:4-dimethoxyphenyl,[9,10,11] red. Curiously, diphenyl-*m*-nitrophenyl[6] gives an orange coloration in sulphuric acid.

3-*Chloro*-5:6-*diphenyl*-1:2:4-*triazine* (VI). A mixture of 3-hydroxy-5:6-diphenyl-1:2:4-triazine (140 g, m.p. 224–226°) and phosphoryl chloride (280 c.c.) was heated in an oil bath (150°) until evolution of hydrogen chloride ceased (*c.* 50 min). The cooled mass was added with stirring to about 3 kg of crushed ice and the yellow solid collected and washed with water. It was thrice triturated with excess of 2% aqueous sodium hydroxide at 50°, collected, and washed (148 g, m.p. 147–149°). The pure substance crystallised from benzene had m.p. 156–157° and gave a crimson solution in sulphuric acid (Found: C, 67·4; H, 3·9; N, 15·3; Cl, 12·9. $C_{15}H_{10}N_3Cl$ requires C, 67·3; H, 3·8, N, 15·6; Cl, 13·2%).

[19] P. P. T. Sah and T. S. Ma *Sci. Rep. Nat.* Tsing Hua Univ. **2**, 143 (1933).
[20] F. L. Pyman *J. Chem. Soc.* **123**, 3372 (1923).
[21] M. A. Kung and K. Koberle D. R. P. 549, 969 (1929).
[22] F. E. Francis and O. C. M. Davis *J. Chem. Soc.* **85**, 259 (1904).
[23] O. Diels and M. Lieberman *Ber.* **36**, 3193 (1903).

The reaction of this substance (0·5 g) with methanol, ethanol, and propanol (100 c.c.) at the boiling-point was followed by titration. In the cases of the two simpler alcohols, the reaction was completed in 4·5 hours. The formation of the ethoxy derivative was only a little slower than that of the methoxy compound. The reaction with propanol proceeded at about two-thirds of the rate, and 64% had reacted after 4·5 hours. The *methoxy diphenyl*-1:2:4-*triazine hydrate* had m.p. 221–222° (Found: C, 68·3; H, 5·1; N, 15·1. $C_{16}H_{15}O_2N_3$ requires C, 68·4; H, 5·4; N, 14·9%), whilst the *ethoxy-derivative* (VII) had m.p. 220–221° (Found: C, 69·3; H, 5·9; N, 14·1. $C_{17}H_{17}O_2H_3$ requires C, 69·3; H, 5·8; N, 14·2%). These substances crystallised on concentration of the respective solutions. They are slowly dissolved on boiling with dilute aqueous sodium hydroxide, and on acidification of the solution the 3-hydroxy-5:6-diphenyl-1:2-triazine was recovered.

3-*Hydrazino*-5:6-*diphenyl*-1:2:4-*triazine* (VIII, R = NH·NH_2). A mixture of chlorodiphenyl-1:2:4-triazine (5·4 g), hydrazine hydrate (3 c.c. of 90%) and pyridine (10 c.c.) was boiled for an hour. The precipitate after the addition of water was collected and crystallised from ethanol; yellow needles m.p. 171–173° (Found: C, 68·5; H, 5·0; N, 27·0. $C_{15}H_{13}N_5$ requires C, 68·0; H, 5·0; N, 26·4%). The solution in sulphuric acid had a crimson colour.

5:6-*Diphenyl*-1:2:4-*triazine* (VIII, R = H). The above hydrazine (0·5 g) in acetic acid (20 c.c. of 10%) was oxidised by the addition of cupric sulphate (1·0 g) dissolved along with sodium acetate (1·0 g) in water (10 c.c.). After 12 hours in the cold, the product (0·15 g) was isolated by means of ether and crystallised from aqueous ethanol; yellow plates, m.p. 112–115° (Found: C, 77·0; H, 4·6; N, 17·7. $C_{15}H_{11}N_3$ requires C, 77·3; H, 4·8; N, 18·0%). The solution in sulphuric acid had a crimson colour.

3-*Phenylhydrazino*-5:6-*diphenyl*-1:2:4-*triazine* (VIII, R = NH·NHPh). A mixture of chloro-diphenyl-1:2:4-triazine (20 g), phenylhydrazine (20 g), and pyridine (55 c.c.) was refluxed for an hour. The product was crystallised from toluene, m.p. 197–198°. (Found: C, 74·7; H, 5·2; N, 20·4. $C_{21}H_{17}N_5$ requires C, 74·4; H, 5·1; N, 20·6%). The yellow substance dissolves in sulphuric acid to a crimson solution. The corresponding azo-derivative was presumably formed in the process described below.

5:6:5′:6′-*Tetraphenyl*-3:3′-*di*-1:2:4-*triazinyl* (IX). The above phenylhydrazino-diphenyl-1:2:4-triazine (2·0 g) in acetic acid (10 c.c.) was added to a solution of ferric chloride (2·0 g) in acetic acid (10 c.c.). The resulting black precipitate was collected, washed, and dried; m.p. >280° (decomp.). This material (1·5 g) mixed with copper powder (1·5 g) was strongly heated under a good vacuum. The sublimate and distillate (0·8 g) was triturated with acetic acid and the yellow product crystallised from this solvent (85%), m.p. 219–222° (Found: C, 77·4; H, 3·9; N, 18·0. $C_{30}H_{20}N_6$ requires C, 77·7; H, 4·3; N, 18·1%). The usual crimson coloration in sulphuric acid was observed.

3-*Amino*-5:6-*diphenyl*-1:2:4-*triazine* (VIII, R = NH_2). Chlorodiphenyl-1:2:4-triazine (5·0 g) was heated with 10% ammonia (20 c.c.) for 6 hours at 140° in a sealed tube. The product was purified by solution in dilute hydrochloric acid and recovery on basification with ammonia; yellow needles, m.p. 175°, in agreement with Thiele and Bihan[23] (Found: C, 73·0; H, 4·7; N, 22·0. Calc. for $C_{15}H_{12}N_4$: C, 72·7; H, 4·9; N, 22·5%). The solution in sulphuric acid has a crimson colour.

[23] J. Thiele and R. Bihan *Annalen* **302**, 309 (1898).

Treatment with hydrochloric acid and sodium nitrite gave an immediate precipitate of 3-hydroxy-5:6-diphenyl-1:2:4-triazine, m.p. 220–1°, after crystallisation, and the same on admixture with an authentic specimen.

Reaction of 3-*chloro*-5:6-*diphenyl*-1:2:4-*triazine with Grignard reagents.* (a) An ethereal solution (200 c.c.) of phenylmagnesium bromide (10 g of magnesium and 41 c.c. of bromo-benzene) was gradually added to one of 3-chloro-5:6-diphenyl-1:2:4-triazine (20 g) in benzene (200 c.c.). The mixture was distilled until the boiling point rose to 70°; it was then refluxed for 12 hours. The cooled mixture was added to sulphuric acid (40 g), crushed ice (300 g), and water (200 c.c.), when the benzene layer became deep blue and later red. The benzene solution was separated, washed, dried, and evaporated. The residue (33 g) was distilled at 150°/0·2 mm and afforded 10 g of diphenyl, m.p. 69–71°. It was then dissolved in ether, and on slow evaporation of the solution afforded 1·6 g of kyaphenine (!); m.p. 231–232° after crystallisation from toluene, alone or mixed with a specimen made from benzonitrile.

Further distillation of the mother liquor gave only more diphenyl (5 g) and benzil (3·0 g).

(b) The reaction was carried out as under (a), except that the Grignard solution was made from *p*-bromotoluene (34 g) and magnesium (4·8 g). The cooled reaction product was heated with concentrated hydrochloric acid (30 g), water (30 g), and crushed ice (50 g). A small undissolved portion was collected and crystallised from acetic acid; long red needles with a metallic lustre, m.p. above 280° (Found: C, 62·1; H, 4·6; N, 13·7; Cl, 7·1 (or Br 11·9); residue after combustion, 0·89%). The nature of this by-product could not be ascertained. The benzene solution was washed, dried, and distilled. Ditolyl (11 g, m.p. 118–120°) passed over at 200°/0·2 mm, and the residue (17 g) was dissolved in ether.

Slow evaporation gave crystals (1·2 g), m.p. 130–135°. After recrystallisation from 90% acetic acid, it formed yellow prisms, m.p. 136–137° (Found: C, 81·7; H, 5·5, N, 12·4. $C_{22}H_{17}N_3$ requires C, 81·9; H, 5·3; N, 13·0%). The melting-point was not depressed on admixture with the specimen (see below) made from benzil and *p*-tolu-hydrazide.

3:5:6-*Triphenyl*-1:2:4:*triazine* (III). This was the first representative of the series to be made by the new method, and a better overall yield was obtained by following the direct process as used below for diphenyl-*p*-tolyl-1:2:4-triazine. However, in the earlier stages of the work (cf. also the *m*-nitrophenyl series below) an attempt was made to isolate the intermediate benzoylhydrazone of benzil.

Benzhydrazide (29·5 g) and benzil (50 g) were dissolved by gentle heating in ethanol (200 c.c.), and acetic acid (50 c.c.) added. After keeping for 7 days, the solution was filtered from a sparingly soluble precipitate (*bis*-benzoylhydrazone?), diluted with water, and the resulting solid collected and dried (36·6 g of m.p. 75–109°). After one crystallisation from methanol (sparingly soluble residue), m.p. 123–138°; two more crystallisations, pale yellow needles m.p. 126–128°, unchanged after three further crystallisations. The sparingly soluble residue crystallised from much methanol in colourless, prismatic needles, m.p. 142–143°.

The analyses of these substances were not quite satisfactory and will be re-examined. According to Struve, benzil *bis*-benzoylhydrazone[24] had m.p. 206°. The triphenyl-1:2:4-triazine was obtained by heating the crude mixture with ammonium acetate in

[24] G. Struve *J. Pr. Chem.* (2), **50**, 308 (1894).

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acetic acid solution, as in later examples. The bright yellow base crystallised from benzene-light petroleum (b.p. 40–60°) as dense clusters of needles forming warty aggregates, m.p. 145–146° (Found: C, 81·5; H, 4·8; N, 13·4. $C_{21}H_{15}N_3$ requires C, 81·6; H, 4·8; N, 13·6%). The substance is only weakly basic and dissolves in sulphuric acid to a red solution. It was reduced in boiling acetic acid by means of an excess of zinc dust (5 min) to 2:4:5-triphenyliminazole (lophine). The product was crystallised twice from ethanol in needles, m.p. 273–274°, alone or mixed with an authentic specimen. The yield was quantitative (Found: N, 9·1. Calc. for $C_{21}H_{16}N_2$: N, 9·5%).

5:6-*Diphenyl*-1-3-p-*tolyl*-1:2:4-*triazine* (VIII, R = *p*-C_6H_4·Me). A mixture of benzil (0·5 g) *p*-tolhydrazide (0·8 g), ammonium acetate (3·0 g), acetic acid (5·0 c.c.), and water (0·5 c.c.) was refluxed for 6 hours. The oily product obtained on the addition of water was washed, dissolved in a little acetic acid, when crystals separated on keeping (1·1 g). After recrystallisation from 90% acetic acid, it formed yellow prisms, m.p. 136–137° (Found: C, 81·7; H, 5·5; N, 12·4. $C_{22}H_{17}N_3$ requires C, 81·9; H, 5·3; N, 13·0%). The solution in sulphuric acid had a deep red colour. Another method of preparation of this substance is reported above.

Benzil m-*nitrobenzoylhydrazone*. A mixture of benzil (21 g) and *m*-nitrobenzhydrazide (18 g) was dissolved in acetic acid (100 c.c.) by heating and the solution at once allowed to cool. The crude product (*c.* 30 g) had m.p. 105–115°.

On crystallisation of 4·0 g from alcohol, there was obtained a sparingly soluble residue and 1·8 g, m.p. 142–144°. On recrystallisation, 1·4 g, m.p. 144–145°, and again 1·2 g, m.p. 145–146°. Finally, a crystallisation from toluene raised the m.p. to 145–146° (Found: C, 67·4; H, 4·2; N, 11·2. $C_{21}H_{15}O_4N_3$ requires C, 67·7; H, 4·1; N, 11·2%). The less soluble product (100 c.c. boiling xylene dissolved 0·1 g) had m.p. 223–228°, raised by successive crystallisations from xylene and acetic acid to m.p. 231–233° (Found: C, 59·7; H, 4·3; N, 13·1%). These are far from the anticipated values for the *bis*-hydrazone (approx. correct for $+3H_2O$) and are in agreement with $C_{21}H_{18}O_6N_4$ (C, 59·8; H, 4·3; N, 13·2%) which could be tri-*m*-nitrobenzylamine, but the matter requires further investigation.

3-m-*Nitrophenyl*-5:6-*diphenyl*-1:2:4-*triazine* (VIII, R = *m*-C_6H_4·NO_2). A mixture of the above-described crude benzil *m* nitrobenzoylhydrazone (14·6 g) with ammonium acetate (20 g) and acetic acid (50 c.c.) was boiled for 10 min. The product crystallised from the hot liquid and after the addition of a little water and cooling was collected (12·0 g). It recrystallised from acetic acid-methanol in pale yellow needles, m.p. 197° (Found: C, 70·9; H, 4·0; N, 15·9. $C_{21}H_{14}O_2N_4$ requires C, 71·2; H, 4·0; N, 15·9%). The substance gives an orange-coloured solution in sulphuric acid.

3-(4′-*Chlorophenyl*)-5:6-*diphenyl*-1:2:4-*triazine*. Ammonium acetate (5 g) was added to a hot solution of benzil (0·6 g) and *p*-chlorobenzhydrazide (0·5 g) in acetic acid (10 c.c.), and the mixture refluxed for half an hour. On cooling, an oily mass separated which, after removal of the supernatant, was triturated with light petroleum (b.p. 80–100°). The solid so obtained was collected, and crystallised from alcohol, forming yellow, prismatic needles, m.p. 134–135° (Found: C, 73·7; H, 4·2; N, 12·3; Cl, 9·7. $C_{21}H_{14}N_3Cl$ requires C, 73·4; H, 4·1; N, 12·2; Cl, 10·3%).

The solution in concentrated sulphuric acid had a cherry-red colour.

3-(4′-*Hydroxyphenyl*)-5:6-*diphenyl*-1:2:4-*triazine*. A mixture of benzil (4 g)

p-hydroxybenzhydrazide (3 g),[25] acetic acid (50 c.c.), and ammonium acetate (40 g) was refluxed for half an hour, during which time the almost pure product began to separate. The solid was collected from the cooled mixture and dried at 100° (4·5 g); m.p. 250–253°. Crystallisation from ethyl acetate afforded light yellow, fluffy needles, m.p. 254–255·5° (Found: C, 77·8; H, 4·8; N, 12·3. $C_{21}H_{15}ON_3$ requires C, 77·5; H, 4·6; N, 12·9%).

The solution in concentrated sulphuric acid had a blood-red colour.

Acetyl derivative. A mixture of the triazine (0·5 g), acetic acid (25 c.c.), and acetic anhydride (5 c.c.) was refluxed for 4 hours. *The product* was collected and crystallised from acetic acid as yellow, irregular plates, m.p. 175–176° (Found: N, 11·6. $C_{23}H_{17}O_2N_3$ requires N, 11·4%).

Reduction of 3-(4′-*hydroxyphenyl*)-5:6-*diphenyl*-1:2:4-*triazine to* 2-p-*hydroxyphenyl*-4:5-*diphenyliminazole.* Zinc dust (2 g) was gradually added to a stirred suspension of the above triazine (0·5 g) in hot acetic acid (10 c.c.), when a clear solution was obtained. The mixture was heated on the steam-bath for about an hour. The solution was decanted from the excess of zinc, diluted with water, and made alkaline by addition of aqueous ammonia. The solid was collected, washed, and crystallised from aqueous alcohol, from which the product separated as pale yellow clusters of needles, m.p. 252–253°, alone or when mixed with an authentic specimen of 4:5-diphenyl-2-*p*-hydroxyphenylglyoxaline prepared by the method of Japp and Robinson,[26] as modified by Cook and Jones.[6]

3-(4′-*Aminophenyl*)-5:6-*diphenyl*-1:2:4-*triazine.* Ammonium acetate (20 g) was added to a hot solution of benzil (2 g) and *p*-aminobenzhydrazide (1·44 g)[27] in acetic acid (20 c.c.), and the mixture boiled under reflux for 15 min. *The product* was isolated in the usual manner. On crystallisation from acetic acid-alcohol, yellow, prismatic needles were obtained; m.p. 218–219° (yield, 2 g) (Found: C, 77·7; H, 5·4; N, 16·8. $C_{21}H_{16}N_4$ requires C, 77·8; H, 4·9; N, 17·3%).

The solution in concentrated sulphuric acid had a cherry-red colour.

Acetyl derivative. The triazine (0·8 g) was boiled with acetic acid (10 c.c.) and acetic anhydride (3 c.c.) for about an hour. After cooling, the solid was collected and crystallised from acetic acid, being so obtained in light yellow, fluffy needles, m.p. 264–265° (Found: C, 75·4; H, 4·9; N, 15·0. $C_{23}H_{18}ON_4$ requires C, 75·4; H, 4·9; N, 15·3%).

3-(4′-*Nitrophenyl*)-5:6-*diphenyl*-1:2:4-*triazine.* When a mixture of benzil (0·5 g) *p*-nitrobenzhydrazide (0·43 g), acetic acid (10 c.c.), and ammonium acetate (5 g) was refluxed for 20 min, the product separated as a crystalline precipitate. This was collected and recrystallised from acetic acid and so obtained in golden yellow needles, m.p. 200–201° (yield, 0·6 g) (Found: C, 71·4; H, 3·8; N, 15·6. $C_{21}H_{14}O_2N_4$ requires C, 71·2; H, 4·0; N, 15·8%).

In concentrated sulphuric acid the usual cherry-red coloration developed.

3-(3′-*Methoxyphenyl*)-5:6-*diphenyl*-1:2:4-*triazine.* Ammonium acetate (5 g) was added to a hot solution of benzil (0·5 g) and *m*-methoxybenzhydrazide (0·4 g) in acetic acid (10 c.c.), and the mixture refluxed for 20 min. After cooling, water was added and the pasty mass which separated was triturated with alcohol-light petroleum

[25] J. T. Hewitt and T. F. Winmill *J. Chem. Soc.* **91,** 446 (1907); G. Struve and R. Radenhausen *J. Pr. Chem.* (2) **52,** 236 (1895).
[26] F. R. Japp and V. Robinson *Ber.* **15,** 1268 (1882).
[27] D. Vorländer and F. Meyer *Annalen* **320,** 136 (1901); T. Curtius *J. Pr. Chem.* (2) **95,** 327 (1917).

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(b.p. 60–80°). The solid which then separated was collected, and crystallised from alcohol-light petroleum (b.p. 60–80°), being so obtained in yellow needles, m.p. 129–130° (yield, 0·5 g) (Found: C, 78·2; H, 5·2; N, 11·9. $C_{22}H_{17}ON_3$ required C, 77·9; H, 5·0; N, 12·4%).

A blood-red coloration was obtained in concentrated sulphuric acid solution.

3-(3′:4′-*Dimethoxyphenyl*)-5:6-*diphenyl*-1:2:4-*triazine*. A solution of benzil (0·5 g), veratr-hydrazide (0·47 g), and ammonium acetate (5 g) in acetic acid (10 c.c.) was boiled for about 15 min under reflux. The solid that separated was collected and crystallised from acetic acid-alcohol, being obtained in yellow needles, m.p. 177–178° (yield, 0·66 g) (Found: C, 74·7; H, 5·3; N, 11·5. $C_{23}H_{19}O_2N_3$ requires C, 74·8; H, 5·2; N, 11·4%).

The concentrated sulphuric acid solution had a dark brown colour.

3-(2′:4′-*Dimethoxyphenyl*)-5:6-*diphenyl*-1:2:4-*triazine*. A mixture of benzil (0·5 g), 2:4-dimethoxybenzhydrazide (0·47 g), ammonium acetate (5 g), and acetic acid (15 c.c.) was refluxed for 20 min, when a solid separated and after cooling was collected. The base crystallised from acetic acid as yellow needles, m.p. 167–168° (yield, 0·65 g) (Found: C, 74·9; H, 4·9; N, 11·6. $C_{23}H_{19}O_2N_4$ requires C, 74·8; H, 5·2; N, 11·4%).

The solution in concentrated sulphuric acid had a dark brown colour.

3-(3′:4′:5′-*Trimethoxyphenyl*)-5:6-*diphenyl*-1:2:4-*triazine*. Benzil (0·5 g) and O-trimethylgallhydrazide (0·55 g) were dissolved in acetic acid (10 c.c.), ammonium acetate (5 g) added, and the solution was refluxed for 15 min. The solid which separated on cooling was collected and crystallised from acetic acid-alcohol, giving yellow needles, m.p. 158–159° (yield, 0·6 g) (Found: C, 72·3; H, 5·1; N, 10·0. $C_{24}H_{21}O_3N_3$ requires C, 72·2; H, 5·3; N, 10·5%).

A blood-red coloration was developed in concentrated sulphuric acid.

5:6-*Diphenyl*-3-(3′:4′-*methylenedioxyphenyl*)-1:2:4-*triazine*. Ammonium acetate (10 g) was added to a hot solution of benzil (1 g) and piperonhydrazide (0·9 g) in acetic acid (20 c.c.). The mixture was boiled under reflux for about 20 min during which time a solid separated. After crystallisation from acetic acid-alcohol it formed yellow needles, m.p. 159–160° (yield, 1·3 g) (Found: C, 74·9; H, 3·9; N, 12·1. $C_{22}H_{15}O_2N_3$ requires C, 74·8; H, 4·3; N, 11·9%).

The substance gave a dark brown solution in concentrated sulphuric acid.

3-α-*Furyl*-5:6-*diphenyl*-1:2:4-*triazine*. A solution of benzil (0·5 g), 2-furhydrazide (0·3 g), and ammonium acetate (5 g) in hot acetic acid (15 c.c.) was refluxed for 20 min, when a solid separated. The substance crystallised from acetic acid-alcohol in yellow needles, m.p. 181–183° (yield, 0·4 g) (Found: C, 76·3; H, 4·2; N, 13·7. $C_{19}H_{13}ON_3$ requires C, 76·3; H, 4·4; N, 14·1%).

The solution in concentrated sulphuric acid had a blood-red colour.

1-*Aminoanthraquinone*-2-*carboxylic acid hydrazide*. Methyl 1-aminoanthraquinone-2-carboxylate was prepared[28] by heating 1-aminoanthraquinone-2-carboxylic acid with methyl hydrogen sulphate at 140° for half an hour. After crystallisation from acetic acid it formed red needles, m.p. 224–226°.

This ester (4 g) was dissolved in hot pyridine (30 c.c.), hydrazine hydrate (16 c.c. of 90%) added, and the mixture was boiled under reflux in an oil-bath at 120–130° for 3 hours. The solid which separated on cooling was collected, washed, dried at 100° (2·4 g; m.p. 225°, decomp.), and crystallised from pyridine, forming brown needles,

[28] D.R.P. 609,401 *Frdl.* **21**, 1031 (1934).

m.p. 230° (decomp.) (Found: C, 64·1; H, 4·4; N, 15·0. $C_{15}H_{11}O_3N_3$ requires C, 64·1; H, 3·9; N, 15·0%).

3-(1′-*Amino*-2′-*anthraquinonyl*):5:6-*diphenyl*-1:2:4-*triazine* (X, R = H). A mixture of 1-aminoanthraquinone-2-carboxylic acid hydrazide (9 g), benzil (9 g), acetic acid (225 c.c.), and ammonium acetate (18 g) was heated under reflux for 2 hours. After cooling, the solid which separated was collected, washed, and dried at 110° (9 g, m.p. 232–234°). On crystallisation from pyridine, the substance formed brown needles, m.p. 236–237·5° (Found: C, 76·6; H, 4·2; N, 12·0. $C_{29}H_{18}O_2N_4$ requires C, 76·7; H, 4·0; N, 12·3%).

The substance dissolved in concentrated sulphuric acid to a yellow solution.

3-(1′-*Benzoylamido*-2′-*anthraquinonyl*)-5:6-*diphenyl*-1:2:4-*triazine*. The above triazine (0·6 g), pyridine (10 c.c.), and benzoyl chloride (0·5 c.c.) were heated together in an oil-bath at 124–135° for four hours. After cooling, water was added and the precipitate separated, collected, washed, and crystallised from acetic acid, being obtained in golden yellow, irregular plates, m.p. 275–277° (Found: N, 10·5. $C_{36}H_{22}O_3N_4$ requires N, 10·0%).

Its solution in concentrated sulphuric acid was red in colour.

3-(1′-*Amino*-4′-*bromo*-2′-*anthraquinonyl*)-5:6-*diphenyl*-1:2:4-*triazine*. The triazine (1 g) was dissolved in pyridine (10 c.c.), and bromine (1 c.c.) added very cautiously to the lukewarm solution and the mixture then heated on a steam-bath for about an hour.

The solid which separated was collected, washed with sodium hydrogen sulphite solution and again with water. Crystallisation from pyridine afforded violet needles (0·8 g), decomposing gradually at 250° (Found: Br, 15·0. $C_{29}H_{17}O_2N_4Br$ requires Br, 15·0%).

A yellowish-orange coloration developed in concentrated sulphuric acid.

When in another experiment the triazine (1 g) was suspended in hot acetic acid (75 c.c.) a solution of bromine (1 c.c.) in acetic acid (4 c.c.) added, and the mixture heated under reflux until the evolution of hydrobromic acid ceased (7 hours) the reaction took a different course. After cooling, the solid which separated was collected, washed with bisulphite solution and finally with water. On crystallisation from pyridine, yellow irregular crystals, decomposing above 340°, were obtained. (Found: C, 63·1; H, 2·9; N, 6·8; Br, 18·5%). The substance dissolved in concentrated sulphuric acid with an orange coloration. The structure of this compound is not yet known.

The authentic bromo-derivative could not be brought into reaction with *p*-toluidine at 200–210° (6 hours) in the presence of sodium and cupric chloride.

Ethyl 1:4-*Diaminoanthraquinone*-2-*carboxylate*. A slow stream of hydrogen sulphide was passed through a suspension of 1-amino-4-nitroanthraquinone-2-carboxylic acid (5 g)[29] in water (255 c.c.) and aqueous ammonia (120 c.c., *d* 0·88) for 40 min when the original reddish-brown solution had turned dark blue. The mixture was kept at room temperature for some time, and the excess of ammonia and hydrogen sulphide were then removed by boiling the solution. The clear solution was filtered hot from free sulphur and acidified with acetic acid. The diamino-acid which separated was collected, washed, and dried at 100° (4 g; m.p. 330°). The substance crystallised from nitrobenzene at 170–180° in blue needles with a copper-bronze lustre, m.p. 340°,

[29] D.R.P. 279,866 *Frdl.* **12**, 420 (1914).
[30] D.R.P. 293,100 *Frdl.* **12**, 445 (1914).

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alone or when mixed with an authentic specimen. 1:4-Diaminoanthraquinone-2-carboxylic acid (4 g) was dissolved in concentrated sulphuric acid (16 c.c.), and ethanol (4 c.c.) added gradually with care. The mixture was heated on a steam-bath for 8 to 10 hours, cooled, and then poured on crushed ice and basified with potassium carbonate. The solid was collected, washed with hot water, and dried at 100° (2 g; m.p. *c.* 195°). The ester crystallised from acetic acid-alcohol in blue needles, m.p. *c.* 210°, when taken in a preheated bath (Found: C, 65·6; H, 4·5. $C_{17}H_{14}O_4N_2$ requires C, 65·8; H, 4·5%). The substance is soluble in benzene, and in sulphuric acid to a light yellow solution.

1:4-*Diaminoanthraquinone-2-carboxylic acid hydrazide*. Hydrazine hydrate (2·5 c.c. of 90%) was added to a solution of ethyl 1:4-diaminoanthraquinone-2-carboxylate (3·5 g) in hot pyridine (35 c.c.), and the mixture heated on the steam-bath for 4 hours. The almost-pure product, which separated on cooling, was collected, washed, and dried at 100° (2·5 g; m.p. about 265°). On recrystallisation from nitrobenzene at 170°, it formed blue, rectangular plates with copper-bronze lustre, m.p. 275°. (Found: C, 61·1; H, 4·0; N, 17·8. $C_{15}H_{12}O_3N_4$ requires C, 60·8; H, 4·1; N, 18·9%). The substance is insoluble in benzene.

3-(1′:4′-*Diamino*-2′-*anthraquinonyl*)-5:6-*diphenyl*-1:2:4-*triazine* (X, R = NH_2). 1:4-Diaminoanthraquinone-2-carboxylic acid hydrazide (6 g), benzil (4·8 g), acetic acid (420 c.c.), and ammonium acetate (60 g) were heated together under reflux for an hour. After cooling, water (200 c.c.) was added and the solid which separated was collected, washed, and crystallised from acetic acid, being obtained as a blue powder (3 g), m.p. 244–246° (Found: C, 73·3, 73·2; H, 4·2, 4·2; N, 14·8. $C_{29}H_{19}O_2N_5$ requires C, 74·2; H, 4·1; N, 14·9%).

A yellowish-brown coloration was obtained in concentrated sulphuric acid solution.

3-(1′-*Amino*-4′-*benzoylamido*-2′-*anthraquinonyl*)-5:6-*diphenyl*-1:2:4-*triazine*. A mixture of the last-mentioned triazine (1 g), pyridine (8·5 c.c.), and benzoyl chloride (0·33 c.c.) was heated in an oil-bath at 120–130° for 2 hours. The pasty mass obtained on treating the reaction mixture with water was triturated with alcohol, when a solid began to separate. This was collected, washed, and crystallised from acetic acid, giving blue, irregular crystals, m.p. 240–242° (Found: N, 12·3. $C_{36}H_{23}O_3N_5$ requires N, 12·3%). The substance dissolved in concentrated sulphuric acid to a yellowish green solution.

3-(1′:4′-*Dibenzoyldiamido*-2′-*anthraquinonyl*)-5:6-*diphenyl*-1:2:4-*triazine*. The triazine (1 g), pyridine (8·5 c.c.), and benzoyl chloride (1 c.c.) were heated in an oil-bath at 120–130° for 3 hours. On diluting the reaction mixture with water, a pasty mass was obtained which was triturated with alcohol, when a solid separated. The derivative separated from acetic acid in brown, irregular crystals, m.p. about 270° (decomp.). (Found: N, 9·7. $C_{43}H_{27}O_4H_5$ requires N, 10·3%). Its solution in concentrated sulphuric acid had a reddish brown colour.

Phenanthraquinone benzoylhydrazone. This substance was obtained by condensation of equimolecular amounts of phenanthraquinone and benzhydrazide in hot acetic acid, with or without the addition of ammonium acetate.

The derivative crystallised from acetic acid in yellow needles, m.p. 189–190°. (Found: C, 77·5; H, 3·8; N, 9·0. $C_{21}H_{14}O_2N_2$ requires C, 77·3; H, 4·3; N, 8·6%). When this substance (0·5 g) along with ammonium acetate (10 g) in acetic acid

(20 c.c.) was refluxed for 3 hours, a new substance separated on cooling. This crystallised from nitrobenzene as golden yellow, glistening plates that did not melt at 360° (Found: C, 87·6; H, 4·0; N, 8·6%). The possible nature of this oxygen-free compound is discussed in the Introduction. It dissolved in sulphuric acid to a deep-blue solution.

Phenanthraquinone p-*aminobenzoylhydrazone*. This derivative obtained in hot acetic acid solution, with or without ammonium acetate, crystallised from pyridine in brown needles exhibiting a green lustre (Found: C, 74·8; H, 4·7; N, 12·2. $C_{21}H_{15}O_2N_3$ requires C, 73·9; H, 4·4; N, 12·3%). On continued refluxing with acetic acid and ammonium acetate, *phenanthraquinone* p-*acetamidobenzoylhydrazone* was produced. This derivative crystallised from pyridine in pale-orange needles, m.p. 257–259°. A better yield was obtained on conventional acetylation by heating the aminobenzoylhydrazone with acetic acid and acetic anhydride; mixed m.p. 257–259° (Found: N, 10·5. $C_{23}H_{17}O_3N_3$ requires N, 10·0%).

Improved preparation of 9-*phenanthrol*. A mixture of phenanthraquinone benzoylhydrazone (1 g) and aqueous potassium hydroxide (250 c.c. of 5%) was refluxed for 5 hours. The hot solution was filtered, and acidified with dilute hydrochloric acid after cooling. The solid which separated was collected, washed with sodium hydrogen carbonate solution, and then with hot water. It crystallised from benzene-light petroleum (b.p. 80–100°) in light-brown needles (0·5 g), m.p. 152–153° (Found: C, 86·7; H, 5·1. Calc. for $C_{14}H_{10}O$: C, 86·6; H, 5·2%). On repeated crystallisation, almost colourless needles were obtained. It was soluble in aqueous sodium hydroxide and gave a blue coloration with chloroform and aqueous alcoholic caustic alkali.

Phenanthraquinone monosemicarbazone. A mixture of phenanthraquinone (10 g), acetic acid (120 c.c.), and semicarbazide hydrochloride (5 g in water, 15 c.c.) was refluxed for 3 hours. On concentrating and cooling the solution, yellow needles (9·5 g, m.p. 222°) were obtained. No rise in melting point occurred on recrystallisation from acetic acid (lit., m.p. 220°, decomp.).

3-*Hydroxyphenanthratriazine*. A mixture of phenanthraquinone monosemicarbazone (2 g) and aqueous potassium hydroxide (100 c.c. of 5%) was refluxed for 1½ hours, and the hot solution then filtered, cooled, and acidified with dilute hydrochloric acid. The solid which separated was collected, washed, and dried at 100° (1·5 g, m.p. 288°, decomp.). The substance crystallised from pyridine in yellow needles, m.p. 288°, (decomp.), alone or when mixed with an authentic specimen. It dissolved in concentrated sulphuric acid to a blood-red solution.

3-*Chlorophenanthratriazine*. 3-Hydroxyphenanthratriazine (2 g) and phosphoryl chloride (4 c.c.) were heated together at 140–150° for an hour. After cooling, the mixture was poured on crushed ice, and the resulting solid collected, washed with water until neutral, and then treated thrice with an excess of 2% potassium hydroxide at 50° in order to dissolve the unreacted hydroxytriazine. The residue was washed free from alkali, and crystallised from dioxane forming yellowish brown clusters of needles (1·5 g), m.p. 238–240° (Found: Cl, 13·4. $C_{15}H_8N_3Cl$ requires Cl, 13·4%). The substance dissolves in concentrated sulphuric acid to a blood-red solution.

An attempted condensation at 100–110° of 3-chlorophenanthratriazine with 1-aminoanthraquinone using phenol as the solvent and in presence of fused sodium acetate and cupric chloride afforded a product which crystallised from alcohol as a light yellow powder, m.p. 165–167° (Found: C, 78·2; H, 4·4; N, 13·3. $C_{21}H_{12}ON_3$

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requires C, 78·0; H, 4·0; N, 13·0%). Because of its insolubility in hot or cold alkali, and the analysis, this material is considered to be 3-*phenoxyphenanthratriazine*. When nitrobenzene was used as the solvent, only the original chlorophenanthratriazine could be isolated.

Ethyl p-*acetamidobenzoate*. A mixture of ethyl *p*-aminobenzoate (2 g), acetic anhydride (4 c.c.), and acetic acid (2 c.c.) was refluxed for 2 hours. The solid which separated on addition of water crystallised from benzene as colourless plates, m.p. 101° (Found: C, 63·7; H, 6·2; N, 7·3. Calc. for $C_{11}H_{13}O_3N$: C, 63·8; H, 6·3; N, 6·8%). Reference to the literature showed that this substance has been prepared by two methods, and different melting-points have been reported, namely m.p. 110° [31] and m.p. 181°.[32] Nevertheless, this substance prepared according to the two earlier methods had m.p. 101°.

3-*Hydroxy*-6:11-*diketo*-6:11-*dihydro*-1-*anthra*-(1:2-*d*)-*pyrazole* (XII). Ethyl 1-nitroanthraquinone-2-carboxylate (2 g) was dissolved in pyridine (60 c.c.), hydrazine hydrate (2 c.c. of 90%) added, and the mixture heated on a steam-bath for 2 hours. The solid which separated on cooling was collected (M. L. below), washed, and dried at 100°. The substance crystallised from nitrobenzene in brown needles (0·6 g), decomp. above 300° (Found: C, 68·3; H, 3·1; N, 10·3. $C_{15}H_8O_3N_2$ requires C, 68·2; H, 3·0; N, 10·6%). Soluble in 10% sodium hydroxide to a violet solution.

The same substance was obtained by the action of hydrazine hydrate on 1-nitroanthraquinone-2-carboxyl chloride in nitrobenzene at the room temperature during 12 hours.

3-*Acetoxy*-6:11-*diketo*-6:11-*dihydro*-1-*anthra*-(1:2-d)-*pyrazole*. 3-Hydroxy-6:11-diketo-6:11-dihydro-1-anthra-(1:2-*d*)-pyrazole (0·2 g), acetic acid (10 c.c.), and acetic anhydride (5 c.c.) were heated together for 45 min. After cooling, the solid which separated was collected, washed, and crystallised from acetic acid-alcohol, giving yellow needles, m.p. 230–232°, with previous decomposition (Found: N, 9·2. $C_{17}H_{10}O_4N_2$ requires N, 9·2%).

Ethyl pyrazole-anthrone-2-*carboxylate* (XIII). The mother liquor indicated above was diluted with water. The yellow precipitate which separated was collected, washed, dried at 100° (0·6 g, m.p. 216–218°), and crystallised twice from acetic acid-alcohol, being so obtained in yellow needles, m.p. 221–222° (Found: C, 70·3; H, 3·9; N, 9·7. $C_{17}H_{12}O_3N_2$ requires C, 69·9; H, 4·1; N, 9·6%). It is sparingly soluble in alcohol, and the solution has a green fluorescence. On hydrolysis, the corresponding *acid*, already reported, was obtained, and this had the properties described in the literature.

1-*Aminoanthraquinone*-2-*carboxylic acid*. A slow stream of hydrogen sulphide was passed through a suspension of 1-nitroanthraquinone-2-carboxylic acid (10 g) in water (150 c.c.) and aqueous ammonia (30 c.c., *d* 0·88) for 30 to 40 min when the suspension had become dark brown. The mixture was kept at the room temperature for a few hours, the excess of ammonia and hydrogen sulphide removed by boiling and the hot solution was then acidified with acetic acid. The solid, which was contaminated with free sulphur, was collected, washed, and dried at 100°. As the sodium salt of the amino-acid is soluble only in very dilute alkali, the alkali extraction of the acid from the free sulphur was a tedious procedure. It was found more convenient to dissolve the acid containing free sulphur in concentrated sulphuric acid and to filter

[31] D.R.P. 151,795 *Frdl.* **7**, 644 (1902).
[32] M. Covello *Chem. Zentr.* II, 76 (1939).

through sintered glass, whereby the sulphur remained undissolved. The acid-liquor was then poured on ice and diluted with water. The free amino-acid which separated was collected, washed, and dried at 100°. Crystallisation from nitrobenzene gave brown needles (8 g), m.p. 288–290° (lit., m.p. 286°).

Anhydride of 1-aminoanthraquinone-2 carboxylic acid. Thionyl chloride (1·1 c.c.) was added, with stirring, to a suspension of 1-aminoanthraquinone-2-carboxylic acid (3 g) in nitrobenzene (20 c.c.), and the mixture heated under reflux in a water-bath at 85–90° for 2 hours. The solid which separated on cooling was collected, washed with dry benzene, and crystallised from nitrobenzene, giving brown needles, which did not melt at 360° (Found: C, 72·2; H, 2·7; N, 6·7. $C_{30}H_{14}O_6N_2$ requires C, 72·3; H, 2·8; N, 5·6%). The substance was chlorine-free and was insoluble in aqueous alkali. Its solution in concentrated sulphuric acid exhibited a yellow coloration. On hydrolysis with aqueous potassium hydroxide, it afforded 1-aminoanthraquinone-2-carboxylic acid, m.p. 286–288°, alone or mixed with an authentic specimen.

Action of hydrazine hydrate on the above anhydride. A mixture of the anhydride of 1-aminoanthraquinone-2-carboxylic acid (0·5 g), nitrobenzene (55 c.c.), and hydrazine hydrate (1 c.c.) was heated at 130–140° for 6 hours. After cooling, the solid which separated was collected, washed with benzene, and crystallised from nitrobenzene, being obtained in brown, irregular crystals, which did not melt at 360° (Found: C, 68·9; H, 4·0; N, 9·5%). It dissolved in concentrated sulphuric acid to a yellow solution. The identity of this substance is not known.

The authors are grateful to the University of Bombay for financial assistance to one of them (H. P. V.) and to Imperial Chemical Industries Ltd., Dyestuffs Division, for the provision of anthraquinone derivatives.

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Tetrahedron, 1957, Vol. 1, pp. 119–128. Pergamon Press Ltd., London

ÜBER NOMENKLATURPROBLEME IN DER STEREOCHEMIE

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(*Received* 10 *January* 1957)

Zusammenfassung—Das geschilderte System zur Bezeichung des räumlichen Baues der organischen Moleküle erlaubt auf Grund einer einfachen allgemeingültigen Vereinbarung die Namen der stereoisomeren Verbindungen der verschiedensten Art zu bilden. Diese Bezeichnungen hängen nicht von irgend einem willkürlich gewählten "Schlüssel" ab, sondern beziehen sich unmittelbar auf den räumlichen Bau des Moleküls. Das ist zur Zeit, wo die Methoden zum Studium der absoluten Konifiguration immer sicherer werden,—besonders wichtig.

Die Bezeichnungen können sowohl aus dem Raummodell, so auch aus der Projektionsformel abgeleitet werden, wobei der umgekehrte Ubergang von dem Name zum Modell oder zur Projectionsformel leicht und anschaulich geschieht. Damit ist eine Möglichkeit gegeben, die komplizierte zeichnerische Darstellung von Raumformeln durch einen Namen zu ersetzten. Das ist besonders für Registrier-Zwecke und für andere Fälle wichtig, wo keine Raumformeln und Zeichnungen gebracht werden können.

Es ist auch ein Vorschlag zur Bezeichnung der Konformation organischer Moleküle eingebracht.

Abstract—Based on a simple, universally valid agreement, the system described in this article for the designation of the steric structure of organic molecules provides a nomenclature for a great variety of stereoisomeric compounds. These designations do not depend on an arbitrarily selected "key," but refer directly to the steric structure of the molecule. This is of particular importance at the present time, when the methods for the investigation of absolute configuration are becoming increasingly reliable.

The designations can be derived either from the three-dimensional model or from the projection formula, so that the construction of the model or projection formula from the name is easily done. Thus it becomes possible to replace the complicated diagrammatic presentation of steric formulae by a name. This is of particular importance in filing and in other cases where three-dimensional formulae or diagrams cannot be used.

A proposal is also made for the designation of the conformation of organic compounds.

Im Laufe der geschichtlichen Entwicklung der Stereochemie, die vor einigen Jahren (wenn man als Anfangsdatum die klassichen Arbeiten von L. Pasteur aus dem Jahre 1848 festlegt) in ihr zweites Jahrhundert getreten ist,—fehlte es nicht an Vorschlägen auf dem Gebiete der stereochemischen Nomenklatur.* Es finden sich darunter Vorschläge, die von den prominentesten Gelehrten stammen: es genügt die Namen von A. Baeyer, P. Walden, W. Meyer, E. Fischer zu nennen. Trotzdem fehlt bis zu den heutigen Tagen ein allgemein brauchbares und ein allgemein anerkanntes System, dass die Kennzeichnung des räumlichen Baues der organischen Moleküle in den Benennungen gestatten würde.

Im Jahre 1951 erschien eine Schrift von R. S. Cahn und Ch. K. Ingold,[3] die einen wichtigen Schritt vorwärts auf dem Gebiete der stereochemischen Nomenklatur bedeutete. Während alle vorhergehenden Vorschläge die Bezeichnungen auf die

* Eine kurze Ubersicht über die Entwicklung der stereochemischen Bezeichnungen findet sich in unseren Arbeiten.[1–2]

Projektionsformeln zurückführten,—brachten Cahn und Ingold als erste den prinzipiell wichtigen Vorschlag—die stereochemischen Bezeichnungen direkt auf das Raummodell zu beziehen, ohne dieses Modell zur bedingten Projektionsformel zu reduzieren. Dieser Grundgedanke war überaus wertvoll, doch seine praktische Verwertung wurde durch die verhängnissvolle Lösung einiger zugehöriger Fragen erschwert. Diese Fragen sind: die Form der Bezeichnungen, d.h. die Wahl der Zeichen, die die Besonderheiten des räumlichen Baues veranschaulichen sollen; und die Methoden der Klassifizierung, d.h. die Regeln, auf Grund denrer die Wahl der Bezeichnung geschieht.

Vor einigen Monaten erschien eine neue Schrift von R. S. Cahn, C. K. Ingold, und V. Prelog,[4] in der das System aus dem Jahre 1951 teilweise abgeändert und erweitert wird. Die Abänderung betrifft die Form der Bezeichnungen: mit vollem Rechte verwerfen jetzt die Verfasser die Zeichen *D* und *L*, die ja schon so verschiedentlich in der Stereochemie gebraucht wurden, das ihre Verwendung in einem *neuen* System die Verwirrung noch vergrössern würde. Die Verfasser wählen andere Zeichen, die sie speziell für die Angabe der *absoluten* Konfiguration—also des physikalisch erforschten wirklichen räumlichen Baues der asymmetrischen Moleküle, verwendet sehen wollen. Damit ist eine der schwachen Stellen der Arbeit aus dem Jahre 1951 glücklich aus dem Wege geschafft.

Leider ist aber die zweite schwache Stelle—die Regeln zur Wahl der Bezeichnungen,—geblieben. Wie bekannt ist, ordnen die Verfasser die asymmetrischen Konfigurationen auf Grund der räumlichen Lage der Gruppen an, deren Rangordnung auf Grund einer von besonderen Regeln festgelegten Abzählung der Atomnummern ermittelt wird. Es scheint auf den ersten Blick, als ob sie auch gute Gründe dazu haben: das so geschaffene System ist von den Namen der Verbindungen, von der organisch-chemischen Nomenklatur völlig unabhängig, was nach der Meinung der Verfasser bei der heutigen Verwirrung in der Nomenklatur einen wichtigen Vorteil bedeutet. Uns scheint es aber der wesentlichste Nachteil des Cahn-Ingold-Prelog-System zu sein!

Die Anordnung der Gruppen nach den Atomnummern ist nicht eine Folge irgend eines Naturgesetzes—es ist ein Kunstgriff, der eigentlich ihre *formelle* Systematisierung gestattet. So wird ermöglicht, dass durch die Anwendung gewisser (letzten Endes willkürlicher!) Regeln die Raumstruktur mittels besonderer Zeichen im Namen wiedergegeben wird. Diese Zeichen sind *unbedigt* mit dem Namen, mit der Nomenklatur verbunden. Denn so lange wir das Raummodell oder die zugehörige Projektionsformel vor Augen haben,—*brauchen wir gar keine besonderen Zeichen*, um die Antipoden zu unterscheiden: wir *sehen* diese Unterschiede direkt am Modell oder an der Projektionsformel! Die Notwendigkeit besonderer Bezeichnungen entsteht aber sofort, wenn wir das Modell (die Projektionsformel) durch einen Namen ersetzten wollen. Die stereochemischen Bezeichnungen werden also praktisch nur im Zusammenhang mit einem Namen gebraucht. Es liegt daher durchaus im Wesen der Sache, wenn die Regeln zur Wahl dieser stereochemischen Bezeichnungen mit den allgemeinen Nomenklaturregeln verwandt sind. Besondere, von der Nomenklatur unabhängige Regeln, die von Cahn-Ingold-Prelog eingeführt werden,—bedeuten eine unerwünschte Komplizierung beim praktischen Gebrauch des Systems. Dieser Nachteil des C—I-Systems wurde schon von Freudenberg[5] hervorgehoben.

Wie gesagt, ist es eine wichtige Errungenschaft von Cahn-Ingold, dass sie als erste

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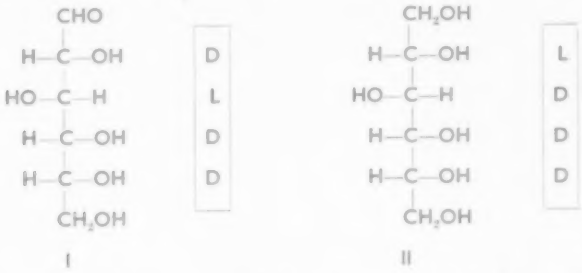
das Raummodell als Grundlage betrachten, und ihre Bezeichnungen nicht auf die Projektionsformel zurückführen, da die Formel ja ganz verschieden geschrieben werden kann. Aber bei der *praktischen Anwendung* eines Bezeichnungssystems ist es wichtig eine Möglichkeit zu haben, die stereochemischen Bezeichnungen nicht nur aus dem Modell, sondern auch aus der Projektionsformel zu ermitteln. In dieser Hinsicht enthält die neue Arbeit von Cahn-Ingold-Prelog einen wichtigen Fortschritt im Vergleich mit der Arbeit aus dem Jahre 1951: jetzt bringen die Verfasser eine "Konversionsregel," die die Bezeichnung mit der Projektionsformel nach Fischer verbindet.

Trotzdem ist aber auch jetzt die Verbindung der C-I-P-Bezeichnungen mit der Projektionsformel nicht immer anschaulich genug. Um ein Beispiel zu bringen, genügt es die Bezeichnungen der asymmetrischen Atome der Glukose (I) und des zugehörigen Hexits (II) zu vergleichen:



I II

Die Anordnung der Gruppen um die asymmetrischen Atome in I und II ist völlig egal. Die beiden unteren Atome erhalten in I und II auch die gleiche Bezeichnung, bei den oberen asymmetrischen Atomen ist aber die Bezeichnung in I und II entgegengesetzt. Die anschauliche Verbindung mit der Projektionsformel fehlt und es ist nicht leicht die nötigen Bezeichnungen zu ermitteln.

Im Jahre 1955 haben wir in Zusammenarbeit mit A. N. Kost und A. M. Zuckerman ein allgemeines System der stereochemischen Bezeichnungen entwickelt, dass unserer Meinung nach die Vorteile des Cahn-Ingold System beibehält, ihre Nachteile aber nicht besitzt.

Wir arbeiten auch am Modell, ähnlich wie es im Jahre 1951 Cahn-Ingold beschrieben haben, gründen aber die Bestimmung der Rangordnung der Gruppen auf den *allgemeinen Regeln der organisch-chemischen Nomenklatur*. Die Bezeichnungen können sowohl aus dem Raummodell, wie aus der Projektionsformel nach Fischer leicht ermittelt werden. Die Grundlagen des Systems sollen nachstehend nochmals kurz geschildert werden. Wegen der Einzelheiten wird auf die früheren Veröffentlichungen verwiesen.[1, 2, 6]

In dem allgemeinsten Falle ist ein asymmetrisches Kohlenstoffatom ein Teil der Kohlenstoffkette—einer acyklischen oder cyklischen, einer Haupt-oder Seitenkette.

[1] A. P. Terentiev, A. N. Kost, A. M. Zuckerman, und V. M. Potapov Nomenclature of Organic Compounds. *Izd. Akad. Nauk. SSSR* Moscow, 94–101 (1955).
[2] A. P. Terentiev, V. M. Potapov, A. N. Kost, und A. M. Zuckerman Vestnik MGU, 1955, No. 6, 97. Teilweise agbedruckt in *Chemische Technik* **7**, 579 (1955).
[3] R. S. Cahn und C. K. Ingold *J. Chem. Soc.* 612 (1951).
[4] R. S. Cahn und C. K. Ingold V. Prelog *Experientia* **12**, 81 (1956).
[5] K. Freudenberg, und W. Lwowski *Lieb. Ann.* **594**, 80 (1955).
[6] A. P. Terentiev, A. N. Kost, A. M. Zuckerman, und V. M. Potapov Vorschläge zur systematischen Nomenklatur organischer Verbindungen. *Izd. INI Akad. Nauk. SSSR* Moscow (1955).

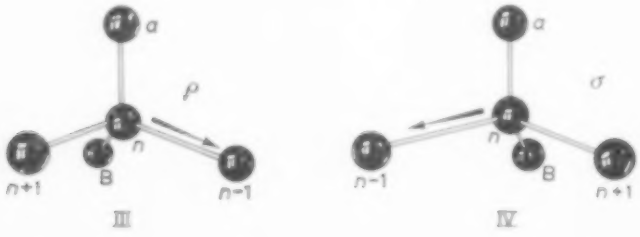
Zwei Valenzen des asymmetrischen Atoms verbinden ihn gewöhlich mit der Kette (Hauptkette), die dritte und vierte Valenz sind durch zwei *verschiedene* Substituenten besetzt. Wenn wir diese Substituenten "*a*" und "*b*" bezeichnen, und die Abschnitte der Hauptkette "$n-1$" (der Anfangsabschnitt der Kette, wo die Numerierung angefangen wurde) und "$n+1$" (der Endabschnitt der Kette), so können die zwei Raummodelle durch folgende Schemen veranschaulicht werden:

Um die Raumstruktur eindeutig im Namen wiederzugeben, muss man die gegenseitige räumliche Lage der vier Gruppen am asymmetrischen Atom angeben. Um die Lage eines Punktes im Raum genau festzulegen, muss man seine Koordinaten bezüglich eines Achsensystems angeben. Wir wählen als eine Ache die Hauptkette mit der ihr nach den gewöhnlichen Nomenklaturregeln erteilten Numerierung der Atome. Somit erhalten wir, ohne neue Regeln einzuführen, zwei genaue "Koordinaten": die Richtung der Achse (Numerierungsrichtung) und die dem asymmetrischen Kohlenstoff zugeteilte Nummer. Um die Raumstruktur eindeutig wiederzugeben, genügt es, die Lage *eines* der beiden Substituenten (*a* oder *b*) hinsichtlich der genannten Koordinaten anzugeben.

Zu diesem Zwecke bedienen wir uns folgender Methode: wir denken sich den Beobachter so auf das asymmetrische Atom gestellt, dass er längs des Valenzstriches disloziert sei, dass das asymmetrische Atom mit einem der Substituenten* verbindet (z.B. "*a*"). Wenn jetzt der Beobachter in der Richtung des Winkels blickt, der durch die Atome $(n-1)-n-(n+1)$ verbindenden Valenzstriche gebildet wird, so weist das Bild in Abhängigkeit von der Konfiguration des asymmetrischen Atoms "*n*" die folgenden Merkmale auf:

(1) Die Numerierungsrichtung kann von links nach rechts verlaufen. Das ist im Schema III der Fall. Solch eine Konfiguration wird mit dem griechischen Buchstaben ρ bezeichnet.

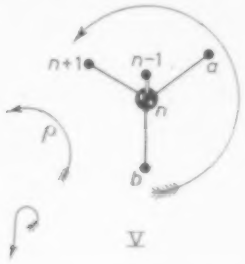
(2) Die Numerierungsrichtung kann, wie das in IV der Fall ist, von rechts nach links verlaufen. Das entspricht der Bezeichnung σ.



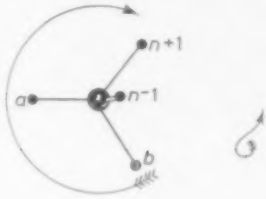
Die Buchstaben ρ und σ sind willkürlich gewählt, namentlich auch deshalb, weil sie bisher für Bezeichnungen in der Nomenklatur organischer Verbindungen nicht angewandt wurden und so keinen Anlass zu Missverständnissen geben können. Ihrer Form nach sind diese Buchstaben antisymmetrisch, was man mit folgender mnemonischer Regel zur Ermittlung der ρ-σ-Bezeichnung in Zusammenhangb ringen kann: stellt man das Tetrahedr des asymmetrischen Atoms so, dass in der auf den Beobachter gerichteten Ecke sich der Anfang der Kette befindet, so wird der Beobachter die drei

* Es soll der Regel nach der "rangälteste" Substituent sein, aber, wie später gezeigt wird, geschieht nichts schlimmes, wenn man auch irrtümlich den anderen Substituent wählt.

restlichen Substituenten in der Basis des Tetraheders, die Ecke (n — 1) umgebend, erblicken (V und VI).



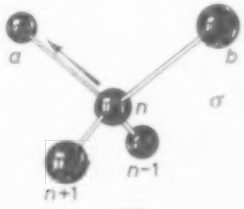
V



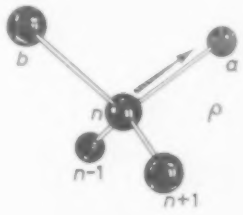
VI

Besitzt das asymmetrische Atom eine ro-Konfiguration (V), so liegen die drei Gruppen in der Reihenfolge der steigenden Rangordnung ($b < a < n + 1$) *gegen* den Uhrzeigersinn—genau so, wie bei dem griechischen Buchstaben ρ eine Bewegung gegen den Uhrzeigersiznn vollzogen wird, wenn man ihn vom Zentralteil zur Peripherie schreibt. Bei der sigma-Konfiguration weist die Lage der Gruppen und die Bewegung beim Schreiben den Uhrzeigersinn auf.

Es ist auch ein dritter Handgriff für die Ermittlung der ρ-σ-Bezeichnung möglich: stellen wir uns vor, dass der Beobachter auf dem asymmetrischen Atom innerhalb des Winkels (109° 28′), der durch die Valenzstriche zu den Substituenten "a" und "b" gebildet ist, steht, und in Richtung des Atoms "$n + 1$" blickt. Bei einer ρ-Konfiguration wird der rangälteste Substituent links vom Beobachter liegen (VII), bei einer σ-Konfiguration rechts (VIII).



VIII



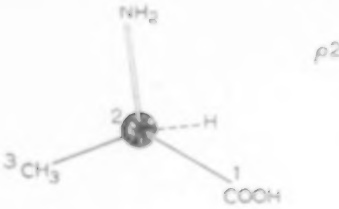
VII

Wenn mann schließlich die ρ-σ-Konfiguration nicht an Hand des Modells, sondern an der Projektionsformel nach E. Fischer bestimmt, so gilt die Regel: bei einer Bewegung längs der Hauptkette gemäss der Numerierungsordnung der Atome wird der rangälteste Substituent des asymmetrischen Atomes bei der ρ-Konfiguration links, und bei der σ-Konfiguration rechts liegen.

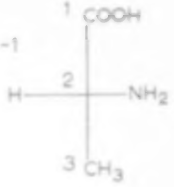
Nebènbei gesagt, es ist die *wirkliche* Fischer'sche Projektion gemeint,[7] also die projezierung einer Konformation, in der die Kohlenstoffkette eine C-ähnliche Form hat und mit dem "offenen" Teil des "C" der Projektionsfläche zugewandt ist. Diese Bemerkung scheint uns notwendig, da in der Literatur auch andersartige Projektionsverfahren irrtümlich als "Fischersche Projektionsformeln" auftreten. Das ist z.B. in dem bekannten Buch von Schlenk und Bergman der Fall.[8]

[7] E. Fischer *Ber.* **24**, 2683 (1891).
[8] W. Schlenk und E. Bergmann *Ausführliches Lehrbuch der organischen Chemie* Bd. I, s. 154. Leipzig-Wien, Franz Deuticke (1932).

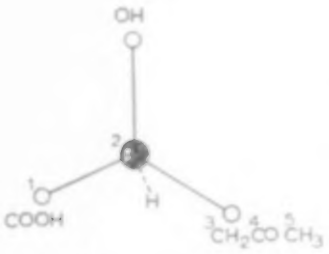
Alle 4 beschriebenen Handgriffe zur Bestimmung der ρ-σ-Bezeichnung sind gleichberechtigt, und führen zum gleichen Resultat. Diese oder jene Methode kann völlig gleichberechtigt angewandt werden, wobei der Anwendende in Abhängigkeit von der Bequemlichkeit des Verfahrens, in Abhängigkeit von der Projektion, oder schliesslich von der Gewohnheit, sich räumliche Modelle in einer bestimmten Weise vorzustellen,—seine Wahl vollziehen kann. Die ermittelte ρ-σ-Bezeichnung wird in dem Namen durch den entsprechenden Buchstaben kennzeichnet, wobei diese Buchstaben vor der Ziffer stehen, die die Lage des rangältesten Substituenten am asymmetrischen Kohlenstoffatom angiebt. So z.B.

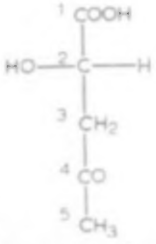


ρ2-Amino-propansäure-1



IX

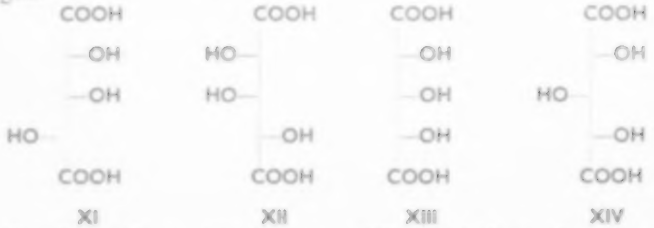




Pentanol-σ 2-on-4-Saure-1

Entsprechend werden auch Verbindungen mit mehreren asymmetrischen Atomen und Asymmetrie in cyklischen Verbindungen bezeichnet, wobei die Hauptregel unverändert bleibt und nur in einigen Fällen noch 2 Zusatzregeln zu berücksichtigen sind. Die ausführliche Beschreibung bringen wir hier nicht und verweisen auf die früheren Veröffentlichungen,[1, 2, 6] die ausserdem noch die logische Erweiterung der Bezeichnungsweise auf molekulare Asymmetrie (Diphensäuren, Spirane, etc.) enthalten.

Wir bringen nur noch einige Beispiele der ρ-σ-Bezeichnung bei komplizierteren Verbindungen.



XI ρ(2,3), σ4-Trioxyglutarsäure
XII σ(2,3), ρ4-Trioxyglutarsäure
XIII ρ(2,3,4), Trioxyglutarsäure
XIV ρ(2,4), σ3-Trioxyglutarsäure

Cahn, Ingold, und Prelog bringen diesen Beispiel auch. Das Inosit mit der Raumformel "*f*" erhielt bei ihnen die Bezeichnung "1*R* : 2*s* : 3*S* : 4*S* : 5*s* : 6*R*",—also

Stereoisomere Inosite

(Cyklohexanhexole – 1;2,3,4,5,6)

(a) ρ(1,2,3,4,5,6)

(b) ρ(1,2,3,4,5), σ6

(c) ρ(1,2,3,4), σ5,6

(d) ρ(1,2,3,5), σ(4,6)

(e) ρ(1,2,4,5), σ(3,6)

(f) ρ(1,2,3), σ(4,5,6)

(g) ρ(1,3,5), σ(2,4,6)

(h) ρ(1,2,4), σ(3,5,6)

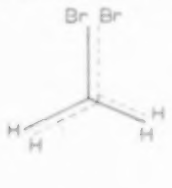
(i) ρ(1,2,4), σ(3,5,6)

im ganzen 4*S*- und 2*R*-Konfigurationen, während das Modell eine gleichmässige Verteilung der Substituenten aufweist (3 oben, 3 unten).

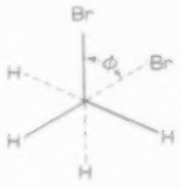
Auch hier ist das ρ-σ-System viel übersichtlicher, da die Bezeichnungen unmittelbar aus der schematischen Formel ersichtlich sind. Die beiden optisch aktiven Inosite (Formeln *h* und *i*) erhalten nach C-I-P die Bezeichnungen 1*R* : 2*S* : 3*S* : 4*S* : 5*S* : 6*R* und 1*R* : 2S : 3S : 4R : 5R : 6R. Es ist dabei nicht ersichtlich, dass es sich um ein Paar von Enantiomeren handelt.

Die Bezeichnungen für Steroide nach dem ρ-σ-System entsprechen vollkommen den bekannten Bezeichnungen nach L. Fieser: es werden nur die Zeichen α-β entsprechend durch ρ-σ ersetzt. Auch hier ist die ρ-σ-Bezeichnung anschaulich mit dem Modell und der schematischen Formel verbunden.

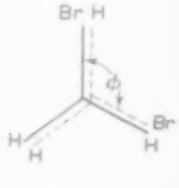
Es ist auch möglich ein System zur Bezeichnung der Konformation (Konstellation) zu schaffen.* Das Prinzip kann man auf dem Beispiel des 1,2-Dibromäthans erklären. Es könnten Konformationsisomere des 1,2-Dibromäthans existieren, die durch folgende Schemen wiedergegeben werden können:



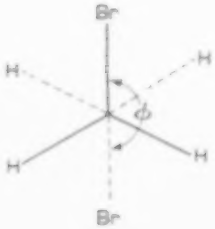
XV



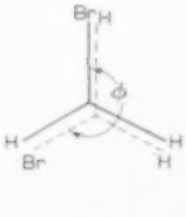
XVI



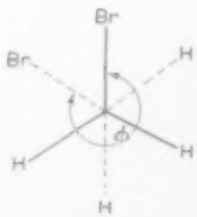
XVII



XVIII



XIX



XX

* Dieser Teil unserer Vorschläge ist früher noch nicht veröffentlicht.

Das Molekül wird hier "von oben"—längs der Achse betrachtet, die beide C-Atome verbindet. Die einzelnen Konformationen unterscheiden sich dabei durch den Winkel φ, den die zum rangältesten Substituent führenden Valenzen bilden. Es wird von uns vorgeschlagen diesen Winkel immer im Uhrzeigersinn abzulesen und die 6 möglichen Konformationen durch die Angabe dieses Winkels wie folgt zu charakterisieren:

	XV	XVI	XVII	XVIII	XIX	XX
Der Winkel φ in Radianeinheiten	0	$1 \cdot \frac{R}{3}$	$2 \cdot \frac{R}{3}$	$3 \cdot \frac{R}{3}$	$4 \cdot \frac{R}{3}$	$5 \cdot \frac{R}{3}$
Bezeichnung	φ^0	φ^1	φ^2	φ^3	φ^4	φ^5

Auf den ersten Blick scheint es, dass die Konformationen XVII und XIX, XVI, und XX gleich sind, aber an Modellen ist es leicht zu sehen, dass alle 6 Konformationen wirklich verschieden sind.

Die einzelnen Konformationen von 1,2-Dibromäthan erhalten somit die Bezeichnungen:

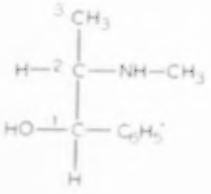
XV 1,2-Dibromäthan-φ^0

XVI 1,2-Dibromäthan-φ^1

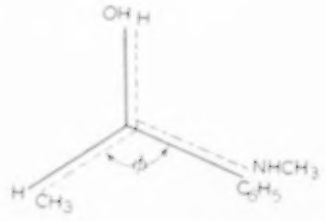
XVII 1,2-Dibromäthan-φ^2

XVIII 1,2-Dibromäthan-φ^3; u.s.w.

Als ein weiteres Beispiel kann das Ephedrin dienen. Wenn man annimmt, dass seine Konformation der Formel XXI entspricht, so würde das zugehörige Modell folgendermassen aussehen:



XXI



Hier sind die rangältesten Substituenten in der Propankette: bei C_1 = Phenyl; bei C_2 = Methyl. Der Winkel φ muss also zwischen ihnen abgelesen werden. Wenn man noch die Konfiguration der 2 asymmetrischen Atome in Betracht zieht, so ergiebt sich die Bezeichnung:

1 φ^2-Phenyl-σ 2-Aminomethyl-propanol-σ1.

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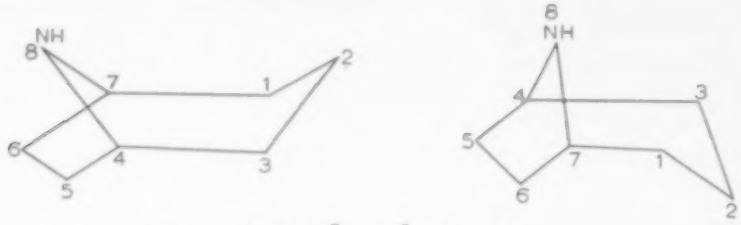
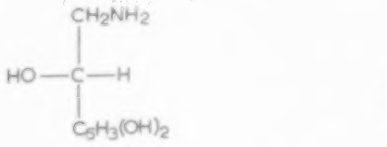
Auch die Konformation komplizierter Ringstrukturen kann mittels der vorgeschlagenen Methode bezeichnet werden, z.B.



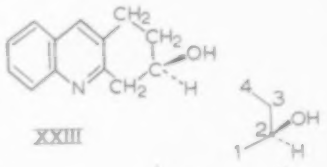
8-Aza-bicyclo [7·8-4] octan-
φ155105155 φ155501151

Die richtigen φ-Indexe können in diesem und ähnlichen Fällen nur an den Modellen ermittelt werden.

Zum Schluss wollen wir nochmals besonders hervorheben, dass das vorgeschlagene System zur Bezeichnung von Stereoisomeren *nicht* fest an irgend ein *bestimmtes* Nomenklatursystem gebunden ist: die ρ-σ-Bezeichnungen können in Verbindung mit einem *jeden* Namen gebraucht werden, der die Struktur der Verbindung abspiegelt. Ein Beispiel dazu: die Verbindungen mit den Projektions formeln XXII und XXIII, die in der Arbeit von C-I-P angeführt sind:



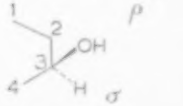
XXII



XXIII

2-Amino-1(3.4-dioxyphenyl)äthanol-ρ
oder:
σ-2-Oxy-β(3.4-dioxyphenyl)-ethylamin

ρ



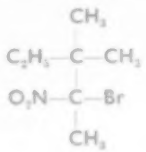
σ

Die Bezeichnung ist bei verschiedener Numerierungsart wohl *verschieden*, aber sie ermöglicht trotzdem einen Übergang zum richtigen Baummodell (oder zur Projektionsformell), und etwas anderes verlangen wir auch nicht von den Bezeichnungen ρ-σ!

Ja, die Hauptkette kann mit Verletzung der Regeln gewählt sein, die Numerierung kann jeglichen Regeln *wiedersprechen*, der Name kann *falsch* gebildet sein,—aber wenn nur der Name, der erhalten wurde, die Strukturformel richtig zu rekonstruieren erlaubt (jeder Organiker kennt Beispiele dazu!)—ist auch das richtige Raummodell herauszubekommen! Noch desto mehr: man kann schliesslich (irrtümlich oder bewusst) auch die Regeln zur Wahl des rangältesten Substituenten verletzen und damit die ρ-σ-Bezeichnung auf das "falsche" Substituent beziehen. Da aber die Bezeichnungen unmittelbar an der Ziffer stehen, die die Lage *dieses* Substituenten

[9] Die Numerierung und Namenbildung gemäss den Vorschlägen von A. P. Terentiev und Mitarbeitern.[9,1,2]
[9] A. P. Terentiev XIV Internationaler Kongress für reine und angewandte Chemie *Referatenband* Zürich, No. 408 (1955).

angiebt,—hat das keine Bedeutung zum Übergang zum *richtigen* Raummodell, z.B. aus dem Namen "ρ3-Brom-3-Nitro-2-Methyl-2-Äthyl-Butan" erhält man die richtige Projektionsformel XXIV, trotzdem dass in der Benennung die Hauptkette falsch gewählt, die Numerierungsregeln verletzt und die Wahl des rangältesten Substituenten am asymmetrischen Kohlenstoff irrtümlich ist.*



XXIV

Diese Beispiele mögen genügen, um zu bestätigen, dass die praktische Verwendung des von uns vorgeschlagenen Systems auf keine Schwierigkeiten wegen der "Verwirrung in der Nomenklatur" stösst: man muss nur immer die *selben Regeln* (können sie noch so falsch sein!), nach denen der Name gebildet wurde, sachgemäss für die Ermittlung der stereochemischen Bezeichnungen anwenden. Uns scheint es praktischer zu sein, als die komplizierten speziel für diesen Fall geschaffenen Regeln von Cahn-Ingold-Prelog zu verwenden.

* Nötigenfalls kann man diese Eigenart des Systems dazu benutzen, um den für eine genetische Reihe wichtigen Substituenten als den "rangältesten" zu wählen und somit die Bezeichnungen einheitlich für die vergleichenden Verbindungen zu gestalten.

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Tetrahedron, 1957, Vol. 1, pp. 129–144. Pergamon Press Ltd., London

ÉTUDES CINETIQUES DANS LE DOMAINE DES DÉRIVÉS POLYCYCLIQUES AROMATIQUES—V

RÉACTIONS DE SOLVOLYSE DE DÉRIVÉS CHLORORÉTHYLÉS D'HYDROCARBURES POLYCYLIQUES AROMATIQUES CONDENSÉS

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(*In revised form* 18 *December* 1956)

Abstract—The solvolyses in different media of six polycyclic aromatic chloromethyl derivatives have been followed conductometrically, according to a previously described method. Kinetic constants and Arrhenius parameters are given.

The results are discussed in terms of mechanistic changes and solvation. It is shown that the equations proposed by Tommila and Dewar to correlate the S_N1 solvolysis rates lead to the same qualitative conclusions.

La présente étude s'intègre dans le cadre de recherches expérimentales entreprises, dans ce laboratoire, sur les réactivités relatives des différents sommets de molécules hydrocarbonées polycycliques aromatiques. Son but tend à préciser les possibilités d'application offertes par les conclusions des travaux théoriques consacrés à ce sujet dans les quinze dernières années (C. A. Coulson, R. Daudel, A. et B. Pullman, R. D. Brown, etc.).

L'interprétation précise des premiers résultats cinétiques relatifs aux solvolyses de dérivés chlorométhylés aromatiques n'a pu être réalisée exclusivement sur la base de l'effet de conjugaison.[1] L'analyse des données expérimentales a montré l'existence de facteurs perturbateurs, parmi lesquels il convient de citer: l'effet stérique, l'effet de solvatation et la variation du mécanisme reactionnel en fonction de la structure.

P. J. C. Fierens *et al.* ont pu préciser, dans une publication antérieure,[2] le mode d'action de l'effet stérique et son importance vis-à-vis de l'effet de conjugaison. Quant à l'effet de solvatation et à la variation du mécanisme réactionnel, leur mode d'action étant complexe, ils nécessitaient une étude plus poussée dont nous rendons compte ici.

1. RESULTATS EXPERIMENTAUX

Nous avons engagé, dans des réactions de solvolyse, les halogénures suivants: le chlorure de benzyle, le chlorométhyl-1-naphtalène, les chlorométhyl-3 et -9-phénanthrènes, le chlorométhyl-9-anthracène et le chlorométhyl-10-benzanthracène-1,2.

Les solvants utilisés sont constitués par des mélanges binaires eau–dioxane, en proportions variables, et un mélange ternaire eau–acide formique–dioxane. La composition des solvants binaires s'étend de (eau 20,5%—dioxane 79,5%) à (eau 79,5%—

* Associé du Fonds National Belge de la Recherche Scientifique (F.R.N.S.).

[1] Part I.—P. J. C. Fierens, H. Hannaert, J. Van Rysselberge et R. H. Martin *Helv.* **38**, 2009 (1955).

[2] Part II.—J. Brändli, E. Dujardin, P. J. C. Fierens, R. H. Martin, et M. Planchon *Helv.* **39** (1956).

dioxane 20,5%), sauf, pour le chlorure de benzyle dont la solvolyse a pu être suivie dans l'eau pure, et, pour les chlorométhyl-9-anthracène et chlorométhyl-10-benzanthracène-1,2 dont les vitesses réactionnelles sont trop élevées pour des teneurs en eau supérieures à 50%.

Le solvant ternaire est de composition (eau 5,3%—acide formique 69,7%–dioxane 25,0%), élargissant un domaine de solvants déjà employé précédemment.[1]

Les mesures cinétiques ont été réalisées à l'aide d'une méthode conductométrique[3] et les constantes de vitesse ont été calculées par la formule du premier ordre. Les concentrations ont été corrigées en tenant compte du coefficient d'expansion thermique des solvants.[1,4]

Les résultats sont consignés dans le tableau 1, où la température ($T°$) est exprimée en degrés centigrades, (n) représente le nombre de mesures, (a) la concentration initiale en halogénure organique, exprimée en mole/litre, et (k) la constante spécifique de vitesse, donnée en sec.$^{-1}$

TABLEAU 1.—RÉACTION: SOLVOLYSE DE $ArCH_2Cl$

$T°$	n	a	k
Chlorure de benzyle			
eau 20,5%—dioxane 79,5%			
79,2	20	0,01728	$1,53 \cdot 10^{-6}$
90,3	20	0,01709	$3,70 \cdot 10^{-6}$
99,3	20	0,01690	$7,47 \cdot 10^{-6}$
110,0	20	0,01673	$1,64 \cdot 10^{-5}$
eau 79,5%—dioxane 20,5%			
25,0	20	—	$2,01 \cdot 10^{-6}$
eau 100%			
25,0	20	—	$1,38 \cdot 10^{-5}$
Chlorométhyl-1-naphtalène			
eau 20,5%—dioxane 79,5%			
74,5	20	0,01738	$3,56 \cdot 10^{-6}$
90,0	20	0,01710	$1,34 \cdot 10^{-5}$
104,0	20	0,01684	$4,07 \cdot 10^{-5}$
111,2	20	0,01672	$7,43 \cdot 10^{-5}$
Chlorométhyl-1-naphtalène (suite)			
eau 49,3%—dioxane 50,7%			
25,0	20	0,01230	$1,01 \cdot 10^{-6}$
36,0	20	0,02058	$3,90 \cdot 10^{-6}$
45,0	20	0,01212	$1,10 \cdot 10^{-5}$
60,0	20	0,02021	$5,41 \cdot 10^{-5}$
eau 65,9%—dioxane 34,1%			
25,0	20	—	$9,26 \cdot 10^{-6}$
eau 79,5%—dioxane 20,5%			
25,0	20	—	$6,13 \cdot 10^{-5}$
39,2	20	—	$3,44 \cdot 10^{-4}$
45,0	20	—	$6,98 \cdot 10^{-4}$
51,0	20	—	$9,37 \cdot 10^{-4}$

[3] P. J. C. Fierens, A. Halleux et H. Hannaert *Bull. Soc. Chim. Belg.* **64,** 191 (1955).
[4] Herz et Lorentz *Z. Phys. Chem.* **A140,** 406 (1929).

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TABLEAU 1—*contd.*

T°	n	a	k
eau 5,3%—acide formique 69,7%—dioxane 25,0%			
40,0	20	0,01863	$2,40 \cdot 10^{-5}$
51,0	20	0,01844	$9,12 \cdot 10^{-5}$
51,0	20	0,01844	$9,19 \cdot 10^{-5}$
60,2	20	0,01829	$2,54 \cdot 10^{-4}$
Chlorométhyl-3-phénanthrène eau 20,5%—dioxane 79,5%			
79,2	18	0,01572	$4,42 \cdot 10^{-4}$
90,3	20	0,01554	$1,76 \cdot 10^{-3}$
99,9	20	0,01537	$3,18 \cdot 10^{-3}$
110,0	20	0,01521	$7,06 \cdot 10^{-3}$
eau 49,3%—dioxane 50,7%			
51,0	20	—	$1,10 \cdot 10^{-5}$
60,0	20	—	$2,81 \cdot 10^{-5}$
60,0	20	—	$2,83 \cdot 10^{-5}$
79,2	20	—	$1,80 \cdot 10^{-4}$
eau 5,3%—acide formique 69,7%—dioxane 25,0%			
40,0	20	0,01436	$9,69 \cdot 10^{-6}$
51,0	20	0,01421	$3,63 \cdot 10^{-5}$
60,2	20	0,01410	$9,46 \cdot 10^{-5}$
74,2	20	0,01391	$4,77 \cdot 10^{-4}$
Chlorométhyl-9-phénanthrène eau 20,5%—dioxane 79,5%			
74,5	20	0,02078	$3,12 \cdot 10^{-4}$
90,3	20	0,01801	$1,28 \cdot 10^{-3}$
99,9	20	0,02022	$3,01 \cdot 10^{-3}$
109,8	20	0,01763	$6,28 \cdot 10^{-3}$

T°	n	a	k
eau 49,3%—dioxane 50,7%			
25,0	20	0,01054	$5,61 \cdot 10^{-7}$
36,0	20	0,01046	$2,46 \cdot 10^{-6}$
45,0	20	0,01039	$7,71 \cdot 10^{-6}$
60,0	20	0,00539	$4,47 \cdot 10^{-5}$
eau 65%—dioxane 34,1%			
25,0	20	—	$4,90 \cdot 10^{-6}$
eau 79,5%—dioxane 20,5%			
25,0	20	—	$3,47 \cdot 10^{-5}$
39,1	20	—	$1,90 \cdot 10^{-4}$
50,0	20	—	$7,32 \cdot 10^{-4}$
50,0	20	—	$7,35 \cdot 10^{-4}$
eau 5,3%—acide formique 69,7%—dioxane 25,0%			
31,0	20	0,02019	$7,12 \cdot 10^{-6}$
40,0	18	0,02002	$2,25 \cdot 10^{-5}$
51,0	17	0,01982	$9,14 \cdot 10^{-5}$
60,2	20	0,01966	$2,49 \cdot 10^{-4}$
Chlorométhyl-9-anthracène eau 20,5%—dioxane 79,5%			
20,0	20	0,01831	$9,46 \cdot 10^{-6}$
30,0	20	0,01815	$3,29 \cdot 10^{-5}$
40,0	20	0,01799	$1,04 \cdot 10^{-4}$
45,0	20	0,01791	$1,77 \cdot 10^{-4}$
eau 34,1%—dioxane 65,9%			
25,0	20	—	$1,26 \cdot 10^{-3}$

TABLEAU 1—*contd.*

$T°$	n	a	k
eau 38,5%—dioxane 61,5%			
25,0	10	—	$3{,}31 \cdot 10^{-3}$
Chlorométhyl-10-*benzanthracène*-1,2			
eau 20,5%—dioxane 79,5%			
40,2	20	0,01356	$2{,}75 \cdot 10^{-5}$
50,0	20	0,01343	$8{,}08 \cdot 10^{-5}$
59,8	20	0,01330	$2{,}12 \cdot 10^{-4}$
70,0	20	0,01316	$5{,}80 \cdot 10^{-4}$
eau 34,1%—dioxane 65,9%			
25,0	20	—	$9{,}46 \cdot 10^{-5}$
eau 38,5%—dioxane 61,5%			
25,0	20	—	$2{,}10 \cdot 10^{-4}$
eau 49,3%—dioxane 50,7%			
18,0	20	—	$7{,}76 \cdot 10^{-4}$
18,0	20	—	$7{,}65 \cdot 10^{-4}$
25,0	20	—	$1{,}92 \cdot 10^{-3}$

Dans le tableau 2, nous mentionnons les valeurs des énergies d'activation (E), exprimées en kilocalories par mole, celles des facteurs de fréquence (log pZ) et les écarts-types correspondants (σ) calculés par la méthode des moindres carrés.[5]

2. DISCUSSION DES RESULTATS

Introduction

Nous avons reporté, dans le tableau 3, les valeurs des divers paramètres théoriques, qui sont associés à chaque sommet de molécules polycycliques aromatiques, à savoir:

(a) les indices de valence libre F_i calculés soit par la méthode de la mésomérie,[6] soit par celle des orbitales moléculaires,[7]

(b) l'indice d'autopolarisabilité λ,[8, 9]

(c) l'énergie de localisation E_L[7,10,11,12] en unités β.

Nous donnons, en outre, le coefficient d'orbitale moléculaire non liante a_0 de l'atome de carbone exocyclique des cations hydrocarbures alternants $ArCH_2^+$, produits par substitution des sommets considérés ci-dessus.[13,14]

On sait que, dans une réaction de solvolyse d'un dérivé chlorométhylé—du type chlorure de benzyle—procédant par un mécanisme S_N1, le pouvoir de conjugaison d'un radical aromatique hydrocarboné se manifeste plus à l'état transitoire qu'à l'état initial. Or, certains auteurs[6,8] ont relié directement ce pouvoir de conjugaison à la

[5] S. Huyberechts, A. Halleux et P. Kruys *Bull. Soc. Chim. Belg.* **64**, 203 (1955).
[6] A. et B. Pullman *Les Théories Electroniques de la Chimie Organique* Masson, Paris (1952).
[7] F. H. Burkitt, C. A. Coulson et H. C. Longuett-Higgins *Trans. Farad. Soc.* **47**, 553 (1951).
[8] C. A. Coulson et H. C. Longuett-Higgins *Proc. Roy. Soc.* **A192**, 16 (1947).
[9] H. C. Longuett-Higgins et C. A. Coulson *J. Chem. Soc.* 971 (1949).
[10] R. Daudel, C. Sandorfy, C. Vorelant, P. Yvan et O. Chalvet *Bull. Soc. Chim. France* **17**, 66 (1950).
[11] F. L. J. Sixma *Rec. Trav. Chim.* P.B. **68**, 915 (1949).
[12] E. C. Kooyman et E. Farenhorst *Trans. Farad. Soc.* **49**, 58 (1953).
[13] H. C. Longuet-Higgins *J. Chem. Phys.* **18**. 275 (1950).
[14] M. J. S. Dewar. Communication personnelle (en cours de publication).

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TABLEAU 2.—RÉACTION: SOLVOLYSE DE $ArCH_2Cl$

Solvant	E	$\sigma(E)$	$\log pZ$	$\sigma(\log pZ)$
Chlorure de benzyle				
eau 20,5%—dioxane 79,5%	20,70	0,03	7,02	0,02
Chlorométhyl-1-naphthalène				
eau 20,5%—dioxane 79,5%	21,82	0,03	8,29	0,02
eau 49,3%—dioxane 50,7%	22,42	0,01	10,45	0,01
eau 79,5%—dioxane 20,5%	22,52	0,03	12,31	0,02
eau 5,3%— ac. formique 69,7%— dioxane 25,0%	24,19	0,04	12,28	0,02
Chlorométhyl-3-phénanthrène				
eau 20,5%—dioxane 79,5%	23,70	0,09	9,38	0,06
eau 49,3%—dixoane 50,7%	22,47	0,02	10,20	0,01
eau 5,3%— ac. formique 69,7%— dioxane 25,0%	24,17	0,11	11,85	0,07
Chlorométhyl-9-phenanthrène				
eau 20,5%—dioxane 79,5%	22,61	0,04	8,72	0,02
eau 49,3%—dioxane 50,7%	24,67	0,07	11,84	0,05
eau 79,5%—dioxane 20,5%	23,62	0,08	12,84	0,06
eau 5,3%— ac. formique 69,7%— dioxane 25,0%	24,53	0,02	12,49	0,08
Chromométhyl-9-anthracène				
eau 20,5%—dioxane 79,5%	21,72	0,03	11,18	0,02
Chlorométhyl-10-benzanthracène-1,2				
eau 20,5%—dioxane 79,5%	21,73	0,04	10,61	0,08
eau 49,3%—dioxane 50,7%	22,63*	0,05	13,89*	0,04

* Ces valeurs n'ont été déterminées qu'à l'aide de constantes spécifiques mesurées à 2 températures (dans tous les autres cas, nous avons fait usage des constantes de vitesse obtenues à 4 températures différentes), aussi n'y a-t-il lieu de voir ici qu'un ordre de grandeur et non des valeurs précises.

grandeur des paramètres théoriques cités. Ainsi, la différence entre l'énergie de résonance du complexe à 'létat transitoire et celle du dérivé à l'état initial est-elle d'autant plus importante que le paramètre choisi, F_i par exemple, caractérisant le sommet de la structure non substituée correspondante possède une valeur plus élevée. Sont directement liées à l'importance de cet effet de conjugaison: celle de la diffusion, dans le radical aromatique, de la charge positive apparaissant à l'état transitoire, et celle de la solvatation qui en résulte. Si, de plus, nous considérons le cas du chlorométhyl-1-naphtalène et du chlorométhyl-9-phénanthrène, dont les structures non substituées correspondantes sont caractérisées par une même valeur des paramètres théoriques,

$ArCH_2Cl$	Famille	ArH correspondant				$ArCH_2^+$ correspondant
		F_i més	F_i (O.M.)	λ_i	E_L	$2\,a_0$
	A	0·073	0·398	0·081	2·54	1·51
		0·075	0·404	0·086	2·48	1·46
		0·172	0·407	0·089	2·41	1·43
	B	0·096	0·452	0·134	2·30	1·34
		0·197	0·452	0·134	2·30	1·36
		0·200	0·451	0·133	2·30	1·34
	C		0·469	0·202	2·19	1·21
	D	0·250	0·514	0·202	2·01	1·07
		0·255	0·520	0·196	2·04	1·12

le problème ne s'en trouve pas simplifié pour autant. En effet, si le pouvoir de conjugaison est identique pour les deux radicaux aromatiques, la différence des dimensions de ceux-ci implique que la densité des charges en un point quelconque des deux noyaux est différente, et, par conséquent, il en est de même du degré de solvatation.

Nous devons donc nous attendre, en comparant le comportement de deux dérivés engagés dans une même réaction, à une variation de l'entropie d'activation, rendant l'interprétation des résultats difficile.

Enfin, le changement de milieux réactionnels nécessaire à l'étude de l'effet de solvatation risque de produire une modification de mécanisme, excluant actuellement toute possibilité de discussion. Nous devons donc déterminer, au préalable, le type de processus auquel on a affaire, et prouver que les modifications apportées à la composition du milieu n'ont aucune influence sur la nature du processus. Dans ce but, nous avons utilisé quatre voies différentes, dont trois avec succès.

1. *Étude des constantes de vitesse par la relation de Winstein et Grunwald*

P. J. C. Fierens *et al.*[15] ont précisé les conditions requises pour l'utilisation de cette relation. La sévérité des hypothèses fondamentales, sur lesquelles celle-ci repose, fait que sa vérification n'est possible qu'au sein de classes restreintes d'halogénures

[15] Mme. L. Wilputte-Steinert et P. J. C. Fierens *Bull. Soc. Chim. Belg.* **64**, 308 (1955).

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organiques, caractérisés entre eux par de fortes analogies de structure. Les dérivés que nous avons étudiés ne présentant pas ces caractéristiques à un degré suffisant, la relation de Winstein et Grunwald s'est avérée inutilisable.

2. *Étude des constantes de vitesse par la relation de Brown et Hudson*

Cette relation, proposée par Brown et Hudson,[16] a été reprise récemment par Tommila,[17] elle est de la forme:

$$\log k = n \log [A] + c^{te} \qquad \text{(i)}$$

où k est la constante de vitesse de la solvolyse, à une certaine température, d'un dérivé halogéné dans un solvant mixte, dont A est le constituant substituant.

A est la concentration en mole/litre de A dans le solvant mixte,

n est l'ordre de la réaction par rapport au constituant A.

La constance, pour un dérivé déterminé et divers milieux, de l'ordre de la réaction par rapport à A, impliquerait une même contribution de la solvatation par ce constituant, à laquelle serait associé un type de mécanisme réactionnel. Une variation de n signifierait une modification de la solvatation, entraînant, suivant Tommila, celle du mécanisme. De la comparaison des valeurs de n obtenues, par exemple, dans les solvolyses monomoléculaires d'un même dérivé dans divers solvants ou de plusieurs dérivés dans un même solvant, on pourrait tirer des renseignements sur l'effet de solvatation. Ne faisant appel à aucune structure de référence, à l'instar de la relation de Winstein et Grunwald, l'équation (i) s'appliquerait particulièrement bien à notre problème.

A l'aide de l'ensemble des résultats obtenus jusqu'à présent dans l'étude de la solvolyse des dérivés chlorométhylés d'hydrocarbures polycycliques aromatiques (cf. tableaux IV et V), nous avons construit les graphiques des figures 1 et 2.

(a) Le passage du solvant (eau 20,5%—dioxane 79,5%) à celui de composition (eau 49,3%— dioxane 50,7%) s'accompagne, pour le chlorure de benzyle et le chlorométhyl-1-naphtalène, d'une augmentation comparable de la vitesse spécifique. Ce point semble montrer que, dans ce domaine, les deux produits réagissent par des processus S_N2 semblables, au cours desquels les contributions du "bond making" l'emportent de beaucoup sur celles du "bond breaking".[18] On sait, en effet, que les différences de F_i, par exemple, provoquent, dans un même solvant, des différences de vitesse spécifique d'autant plus faibles que le facteur "formation" joue, dans le mécanisme réactionnel, un rôle plus important, ceci étant dû à la nature même des états transitoires.

Par contre, le passage du solvant (eau 49,3%—dioxane 50,7%) à celui (eau 65,9% —dioxane 34,1%) provoque, pour le chlorométhyl-1-naphtalène, une augmentation de vitesse spécifique comparable à celle provoquée, pour le chlorure de benzyle, par le passage de (eau 49,3%—dioxane 50,7%) au solvant (eau 79,5%—dioxane 20,5%). Nous avons donc ici une valeur très différente, pour chaque dérivé, de la balance des facteurs "rupture" et "formation", en d'autres termes, le dérivé naphtalènique réagit par un mécanisme plus proche de la S_N1 que celui du chlorure de benzyle.

(b) Des considérations analogues à celles qui viennent d'être exposées montrent

[16] D. A. Brown et R. F. Hudson *J. Chem. Soc.* 3352 (1953).
[17] E. Tommila, M. Tiilikainen, et A. Voipio *Ann. Acad. Sci. Fennicae* A n°65 (1955).
[18] Mme. L. Wilputte-Steinert, P. J. C. Fierens, et H. Hannaert *Bull. Soc. Chim. Belg.* **64,** 632 (1955).

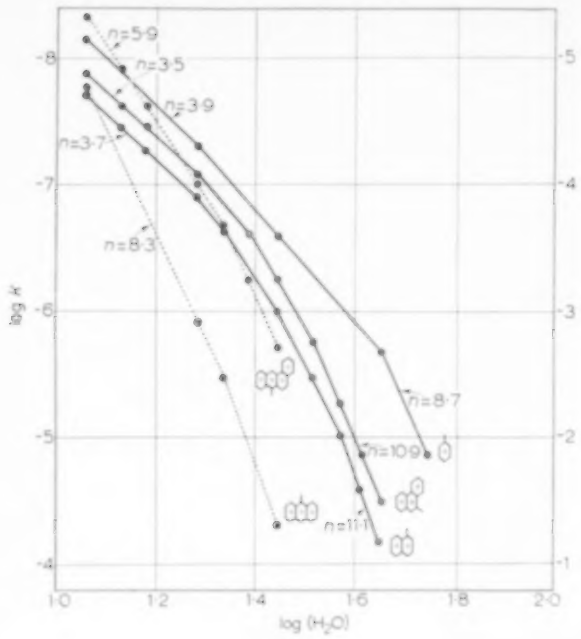

FIG. 1.

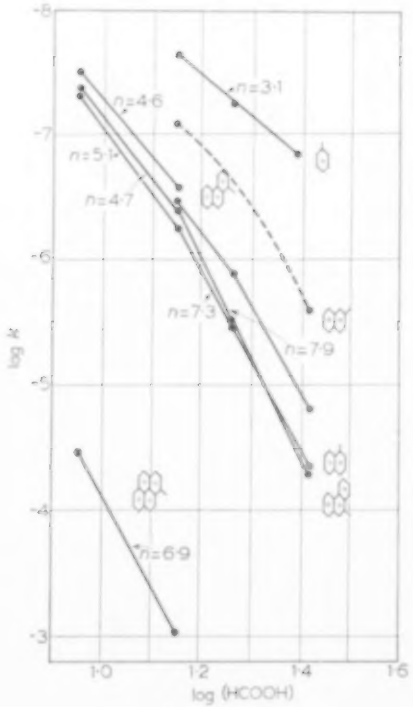

FIG. 2.

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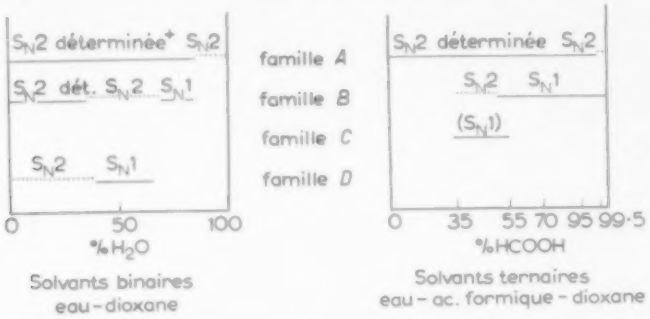
que la différence de comportement entre les deux mêmes dérivés est plus sensible dans les milieux ternaires pauvres en acide formique, ce qui implique plus grande contribution du "bond breaking" vis-à-vis du "bond making" et une tendance plus marquée à se rapprocher du processus monomoléculaire.

(c) Les conclusions tirées des résultats figurant dans les tableaux 4 et 5 peuvent ainsi être schématisées de la manière suivante:



*Nous entendons par S_N2 déterminée un processus auquel correspond une solvatation de type constant caractérisé par une valeur déterminée de la balance "bond breaking–bond making". Il s'agit donc d'un échelon particulier dans la série des mécanismes bimoléculaires, lequel ne coincide pas avec une S_N2 limite.

3. *Étude des constantes de vitesse par la relation de Dewar*

Dans un travail récent, Dewar[14] a tenté d'effectuer le calcul théorique de la variation d'énergie libre d'activation se produisant lorsque, dans des solvolyses monomoléculaires de dérivés $ArCH_2Cl$, on fait varier la nature de Ar. L'expression obtenue pour la constante de vitesse d'une solvolyse monomoléculaire est de la forme:

$$\log k = \log pZ - \frac{1}{2{,}3RT}(\Delta E_\delta + \Delta E_{\text{solvatation}} + 2a_0\beta + A) \qquad \text{(ii)}$$

où ΔE_δ est due à la rupture de la liaison C—Cl,

$\Delta E_{\text{solvatation}}$ est due à la différence des énergies de solvatation entre l'état initial et l'état transitoire,

a_0 est le coefficient d'orbitale moléculaire non liante de l'atome de carbone exocyclique dans le cation $ArCH_2^+$ (cf. tableau 3),

β est l'intégrale de résonance associée à la liaison subissant l'hétérolyse.

Des valeurs de ce dernier paramètre, on pourrait, selon Dewar, tirer des renseignements sur la contribution du "bond breaking" au processus de solvolyse étudié. C'est ainsi que l'auteur établit, à l'aide de résultats expérimentaux, que β est de l'ordre de 30 kcal pour un processus où la contribution du "bond breaking" est, de très loin, la plus importante, alors qu'elle ne serait que de 5 kcal dans un mécanisme où le "bond making" est prédominant. De plus, dans ce dernier cas, les points représentant les dérivés de différentes familles (cf. tableau 3) se placent surune même droite, alors que pour la S_N1, il y a lieu de distinguer plusieurs tronçons parallèles (de pente β), chacun

* Le sens physique de n fera l'objet d'une communication ultérieure, car la constance de n ne nous paraît qu'une condition suffisante à l'existence d'un seul type de processus réactionnel.

se rapportant à une famille. Cette dissociation serait due à une modification constante, pour chaque famille, de l'energie des électrons σ (cf. ΔE_σ). Enfin, l'auteur estime que les variations de log pZ et de $\Delta E_{\text{solvatation}}$ se compensent, lorsque l'on modifie la nature de Ar.

L'interprétation des résultats basée sur la relation (ii) concorde parfaitement avec celle proposée ci-dessus en utilisant la relation (i). Elle met qualitativement en évidence une évolution du processus réactionnel de solvolyse en fonction de la nature de Ar (cf. figures 3 et 4). Toutefois, si l'on peut admettre que, au sein de chaque

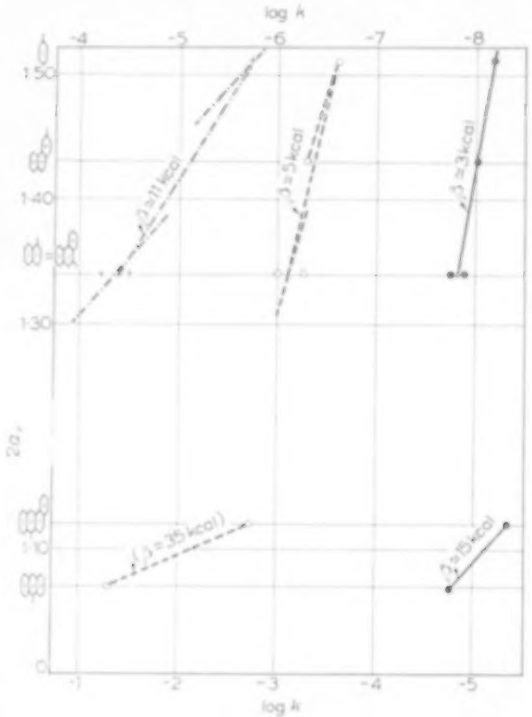


FIG. 3.
——— eau 20,5% dioxane 79,5.
— — — — eau 49,3% dioxane 50,7%.
— . — . — eau 79,5% dioxane 20,5%.

famille, ΔE_σ est indépendant de Ar, l'expérience montre l'existence de l'effet de solvatation, auquel nous avons fait allusion dans l'Introduction, et qui est distinct de celui lié à la variation du mécanisme réactionnel. Cet effet est d'ailleurs responsable de la différence de vitesse existant entre deux dérivés caractérisés par une valeur identique de a_0 et appartenant à une même famille B.

Exemple: dans le solvant (eau 49,3%—dioxane 50,7%) et à 25°, pour le

chlorométhyl-1-naphtalène, log $k = -6{,}00$

chlorométhyl-9-phénanthrène, log $k = -6{,}26$

Cet effet doit, par conséquent, se manifester dans chaque famille, par une variation de la différence entre log pZ *et* $\Delta E_{\text{solvatation}}$, ce qui explique probablement le manque de rigueur dans la linéarité de certaines relations observées.

La vérification de l'équation (ii) et la constance de β qui en découle ne sont donc qu'une condition suffisante à l'existence d'un seul type de processus réactionnel.

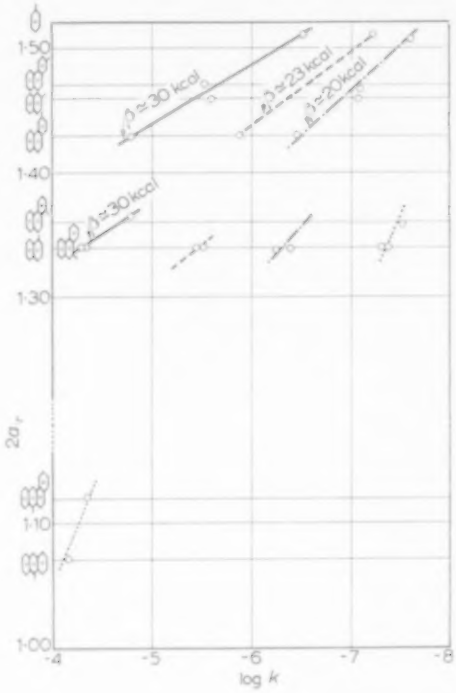


FIG. 4.
——— eau 0.5 % ac. formique 99,5 %.
— — — eau 5,3 % ac. formique 69,7 % dioxane 25,0 %.
— . — . — eau 6,1 % ac. formique 54,1 % dioxane 39,8 %.
. . . . . eau 5,8 % ac. formique 34,0 % dioxane 60,2 %.

4. *Étude des paramètres d'Arrhénius* (*E et log pZ*)

Le lien existant entre ces paramètres et la composition du solvant est représenté, sur les figures 5 et 6, pour tous les produits étudiés.

L'existence, dans quelques domaines de solvants, de relations linéaires entre, d'une part, les valeurs de log k et, d'autre part, la composition de ces milieux et les constantes diélectriques qui les caractérisent, nous a permis l'interpolation de certains de nos résultats expérimentaux. Nous avons pu ainsi compléter le tableau 4 et préciser l'allure des courbes de la figure 5.

(a) Nous pouvons tenter d'expliquer les formes apparemment bizarres de ces dernières en nous basant sur le raisonnement-type appliqué récemment par Tommila, dans un cas similaire.[17] Envisageons les phénomènes caractérisant les solvolyses d'un halogénure hypothétique $ArCH_2Cl$, qui ragirait, dans l'intervalle de (eau 1 %—dioxane

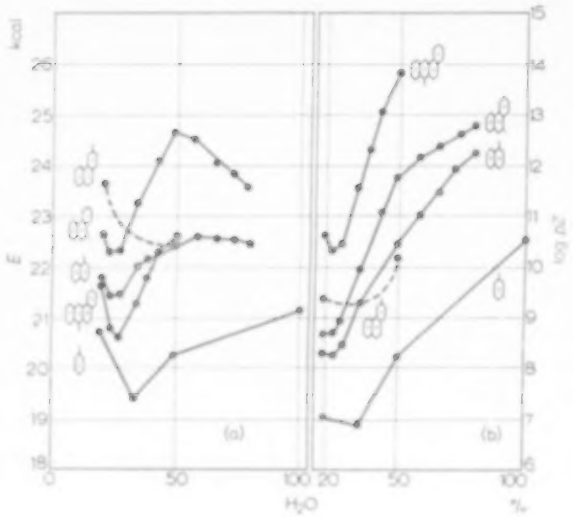


FIG. 5.

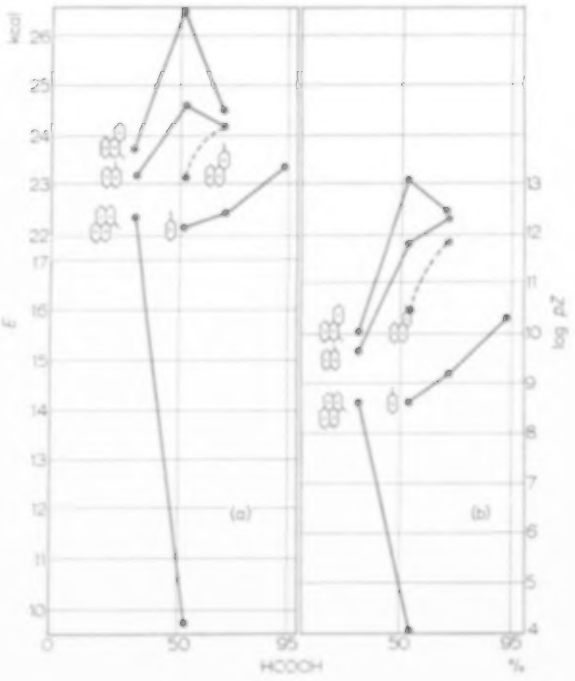


FIG. 6.

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TABLEAU 4.—SOLVOLYSE DE DÉRIVÉS DU TYPE $ArCH_2Cl$ DANS DES SOLVANTS EAU–DIOXANE
(a: volume % en eau)

a	$[H_2O]_{25°}$ mole/litre	Ar / $\log[H_2O]$	fam. A	fam. A	fam. B	fam. B	fam. D	fam. D
			log $k_{25°}$					
20·5	11·48	1·060	-8·17	-8·01	-7·73	-7·87	-4·76	-5·33
24·0	13·47	1·129	–	–	(-7·47)	(-7·63)	–	(-4·93)
27·0	15·17	1·181	–	–	(-7·29)	(-7·45)	–	(-4·63)
34·1	19·23	1·284	(-7·30)	–	(-6·90)	(-7·08)	-2·90	-4·02
38·2	21·57	1·334	–	–	(-6·66)	–	-2·48	-3·68
43·0	24·30	1·386	–	–	–	(-6·60)	–	(-3·27)
49·3	27·86	1·445	-6·60*	-6·29	-6·00	-6·26	(-1·31)	-2·72
58·0	32·78	1·516	–	–	(-5·49)	(-5·76)	–	–
65·9	37·16	1·570	–	–	-5·03	-5·29	–	–
73·0	41·07	1·614	–	–	(-4·60)	(-4·87)	–	–
79·5	44·60	1·649	-5·70	–	-4·21	-4·49	–	–
100·0	55·43	1·744	-4·87*	–	–	–	–	–

Remarques. 1. Les valeurs entre parenthèses ont été obtenues par interpolation (cf. Discussion, § 4) et ne fournissent donc que des ordres de grandeur. 2. Les valeurs marquées * sont relatives à des résultats obtenus par Mme. L. Wilputte-Steinert et P. J. C. Fierens *Bull. Soc. Chim. Belg.* **65**, 719 (1956).

99 %) à (eau 99 %—dioxane 1 %), successivement par différents mécanismes SN_2, puis par un processus monomoléculaire. Dans les solvants très pauvres en eau, le dioxane a tendance à solvater toute la molécule $ArCH_2Cl$ (noyau aromatique et centre réactionnel), tant à l'état initial qu'à l'état transitoire. L'addition d'une faible quantité d'eau augmentera plus la solvatation de l'état transitoire (principalement au niveau du centre réactionnel) que celle de l'état initial, étant donné la plus grande polarité du premier; on notera donc une décroissance de E. Dans ce domaine de solvants, les mécanismes étant bimoléculaires (cf. Discussion, § 2), la différence de polarité envisagée ci-dessus n'est pas très grande. Il en résulte qu'une nouvelle augmentation de la teneur en eau modifiera bientôt la solvatation de l'état initial avec, pour résultat, une croissance de E. La contribution du "bond breaking" devenant progressivement plus importante, au fur et à mesure que le pourcentage en eau est plus élevé, l'état transitoire deviendra plus polaire. Par conséquent, la variation de la solvatation de ce dernier l'emportera à nouveau, graduellement, sur celle de l'état initial. Il arrive un moment où la solvatation de l'état transitoire, au niveau du centre réactionnel, n'est plus modifiée (n = constante) et où toute augmentation nouvelle de la quantité d'eau influencera dès lors la solvatation du noyau aromatique. La substitution, autour du noyau, de molécules d'eau aux molécules de dioxane produit une diminution de l'énergie de solvatation tant de l'état initial que de l'état transitoire. Toutefois, ce dernier étant plus polaire, il y sera moins sensible et l'énergie d'activation décroîtra.

Deux des courbes de la figure 5 illustrent complètement ce schéma théorique, celles des chlorométhyl-1-naphtalène et chlorométhyl-9-phénanthrène; les autres n'en constituent que des fragments.

Tableau 5.—Solvolyse de dérivés du type $ArCH_2Cl$ dans des solvants eau-acide formique–dioxane
(*a*: volume % en eau; *b*: volume % en acide formique)

a		5·8	6·1	5·3	6·4	0·5
b		34·0	54·1	69·7	93·6	99·5
log [HCOOH]		0·955	1·157	1·266	1·395	1·421
log $k_{25°}$	fam. *A*	–	-7·61⁺	-7·25⁺	-6·85⁺	-6·54⁺⁺
	fam. *A*	–	-7·09⁺	–	–	-5·59⁺⁺
	fam. *A*	–	-6·46⁺	-5·88	–	-4·80⁺⁺
	fam. *B*	-7·31⁺	-6·26⁺	-5·47	–	-4·34⁺⁺
	fam. *B*	-7·36⁺	-6·39⁺	-5·51	–	-4·30⁺⁺
	fam. *B*	-7·51⁺	-6·56⁺	–	–	-4·70⁺⁺
	fam. *C*	-4·46⁺	-3·03⁺	–	–	–
	fam. *D*	-4·16⁺	–	–	–	–
	fam. *D*	-4·35⁺	–	–	–	–

Remarques. 1. Les valeurs marquées ⁺ sont tirées de travaux antérieurs.[1] 2. Les valeurs marquées ⁺⁺ nous ont été très aimablement communiquées par le Professeur M. J. S. Dewar.

L'interprétation des variations des valeurs de log *pZ* est analogue à celle avancée pour les modifications de *E*.

(b) Pour compléter l'interprétation donnée en (a), il est utile de considérer le lien existant entre, d'une part, l'énergie et l'entropie de solvatation, et, d'autre part, la structure interne du solvant.

Dans les solvants binaires très riches en dioxane,[19] chaque molécule d'eau exerce un effet inductif maximum sur les molécules non polaires de dioxane, produisant le plus grand nombre possible de "liens" dipôle–dipôle induit. On doit également tenir compte des liaisons d'hydrogène, comme le prouverait l'existence de l'azéotrope (eau 15%—dioxane 85%). La libération des molécules d'eau nécessaires à la solvolyse mettra donc en jeu, dans le domaine (dioxane 100 à 85%), des quantités importantes

[19] R. D. Stallard et E. S. Amis *J. Amer. Chem. Soc.* **74**, 1781 (1952).

d'énergie auxquelles correspondront de faibles énergies de solvatation. Après avoir dépassé la composition azéotropique, l'effet des "liens" dipole–dipôle induit s'affaiblit et celui attaché aux liaisons d'hydrogène est seul à subsister avec, pour conséquence, une augmentation des énergies de solvatation, laquelle porte d'abord sur l'état transitoire, puis sur l'état initial. L'ensemble de ces faits tend à expliquer partiellement la décroissance observée de E_t dans les solvants binaires à teneur en eau inférieure à 30% (quel que soit le produit étudié). Des interactions dipôle–dipôle entre molécules d'eau s'ajouteront, ensuite, progressivement, aux liaisons d'hydrogène, abaissant de nouveau les énergies de solvatation et contribuant aux relèvements des valeurs de E_t observés à partir de (eau 30%). L'importance de cet effet ira croissant avec la teneur en eau.

Un raisonnement identique est applicable à l'étude des variations de l'entropie de solvatation.

CONCLUSIONS

(a) Cette étude attire l'attention sur le fait que les relations de Brown-Hudson et de Dewar, obtenues par des voies toutes différentes, permettent de tirer des conclusions raisonnables quant à la nature du mécanisme de solvolyse d'un dérivé chlorométhylé, dans des conditions expérimentales bien déterminées. Elles montrent plus particulièrement que, pour un solvant donné, l'aptitude à réagir par un processus S_N1 est d'autant plus grande que les dérivés étudiés sont caractérisés, par exemple, par des valeurs plus élevées de l'indice de valence libre dans les hydrocarbures aromatiques polycycliques non substitués correspondants.

(b) Cette étude montre d'autre part qu'une interprétation rigoureuse des résultats cinétiques de solvolyse doit tenir compte des cinq éléments suivants:

1° l'effet de conjugaison,
2° l'effet stérique (cf.[1]),
3° la variation du processus réactionnel,
4° l'effet de solvatation: (a) lié à la variation du processus réactionnel,
(b) lié à la structure du reste Ar,
5° l'énergie des liaisons σ.

Les conditions expérimentales n'ont pas rendu possible, pour un même solvant, les comparaisons, à entropie d'activation constante, des enthalpies d'activation de solvolyse monomoléculaire. En conséquence, les relations de Brown-Hudson et de Dewar permettent une étude des variations d'énergie libre d'activation, dans des conditions telles que, pour chaque cas, ce ne soit qu'un des cinq éléments mentionnés qui intervienne. C'est ainsi que, en absence d'effet stérique (2°), considérant un mécanisme S_N1 (3° et 4°a), on peut *tenter d'interpreter qualitativement les variations des constantes de vitesse* des produits d'une même famille (1° et 5°) en fonction de l'*effet de solvatation lié a la structure du reste Ar* (4°b).

Ce procédé, bien que non rigoureux, ouvre la voie à des recherches complémentaires (en cours de réalisation) permettant, sur un ensemble suffisant de résultats, l'interprétation, à entropie d'activation constante, des variations d'enthalpie en termes d'énergie potentielle.

3. PARTIE EXPERIMENTALE

Tous les renseignements expérimentaux ont déjà fait l'objet de publications antérieures.[1,20]

[20] Mme. L. Wilputte-Steinert et P. J. C. Fierens *Bull. Soc. Chim. Belg.* **64**, 287 (1955).

Nous tenons à témoigner toute notre reconnaissance à Monsieur le Professeur R. H. Martin pour l'intérêt qu'il a porté à la réalisation de ce travail.

Nous remercions aussi très vivement Monsieur le Professeur M. J. S. Dewar qui nous a communiqué avant publication, les conclusions d'une importante recherche effectuée sous sa direction.

Notre gratitude va au Fonds National Belge de la Recherche Scientifique (F.N.R.S.) et à l'Institut pour l'encouragement de la Recherche Scientifique dans l'Industrie et l'Agriculture (I.R.S.I.A.) pour leur appui moral et matériel.

Nous remercions le Centre National de Calcul Mécanique pour le prêt d'une machine à calculer.

Nous remercions aussi le Centre National Belge de Chimie-Physique moléculaire qui nous a fait bénéficier d'un subside.

Nous remercions enfin le Laboratoire de Calcul de l'Université qui s'est chargé des calculs statistiques.

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Tetrahedron, 1957, Vol. 1, pp. 145–157. Pergamon Press Ltd., London

HETEROLYTIC DECOMPOSITION OF ONIUM COMPOUNDS (DIPHENYL HALOGENONIUM AND TRIPHENYLOXONIUM SALTS)

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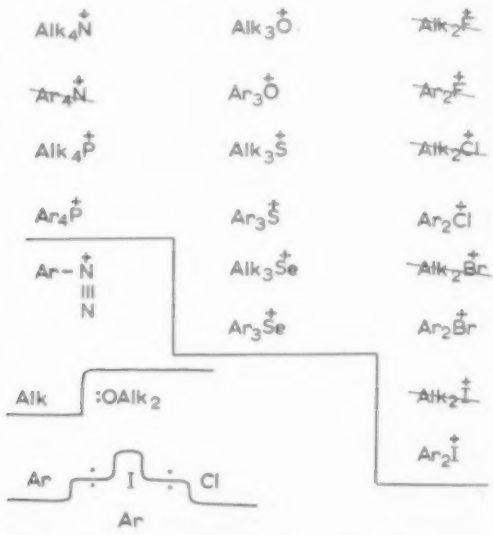
(*Received* 1 *January* 1957)

THE present report deals with the investigation of various types of exchange of aromatic onium compounds. In Table 1 are listed the types of aliphatic and aromatic onium compounds known at present.

TABLE 1



One must add to them aryldiazonium salts, which may be considered as onium compounds of the nitrogen molecule. In exchange reactions, onium compounds, particularly ammonium[1] and oxonium,[2] transfer their aliphatic radicals to the attacking molecule heterolytically (Table 2).

[1] A. E. Porai-Koshits Trudy Leningrad. Khim.-Technol Institute, Vypusk I (1934); D. N. Kursanov and V. N. Setkina *Izvest. Akad. Nauk. SSSR, Otdel. khim. nauk.* 190, 274 (1949); 386 (1950); *Doklady Akad. Nauk SSSR* **65**, 847 (1949); D. N. Kursanov, V. N. Setkina, and V. M. Rodionov *Izvest. Akad. Nauk SSSR, Otdel. khim. nauk.* 228 (1948); D. N. Kursanov and O. M. Shemyakina *Doklady Akad. Nauk SSSR* **62**, 341 (1948); E. Meyer C. A. **5**, 887 (1911); H. R. Snyder *et al.* *J. Amer. Chem. Soc.* **61**, 668, 2895 (1939); **66**, 200, 350 (1944); **67**, 38 (1945); **70**, 1703, 1857, 3855 (1948); **71**, 663 (1949); **73**, 970 (1951).

[2] H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil *J. Prakt. Chem.* **147**, 257 (1937); H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang *J. Prakt. Chem.* **154**, 83 (1939).

TABLE 2

Heterolyse

$(C_6H_5)(CH_3)_2C_6H_5CH_2\overset{+}{N}Cl^- + HOC_6H_5 \longrightarrow C_6H_5CH_2OC_6H_5$

$\longrightarrow ROCH_2OR$

$(C_2H_5)_3O\overset{+}{B}F_4^- + RCOOH \longrightarrow RCOOC_2H_5$

$(C_2H_5)_3O\overset{+}{B}F_4^- + R_3N \longrightarrow [R_3\overset{+}{N}C_2H_5]BF_4^-$

On the other hand, it has been shown previously[3] and by our investigations that aromatic radicals are usually transferred homolytically as free phenyl radicals. Such, for example, is the method of synthesis of aromatic organo-mercuric compounds, discovered in 1929, when decomposing double diazonium salts and mercuric chloride

TABLE 3

$C_6H_5N_2HgCl_3$	+ Cu	$\longrightarrow$	C_6H_5HgCl	Nesmeyanov, 1929
$C_6H_5N_2Cl$	+ Hg	$\longrightarrow$	C_6H_5HgCl	McClure, Lowy, 1931[21]
$(C_6H_5N_2)_2SnCl_4$	+ Sn	$\longrightarrow$	$(C_6H_5)_2SnCl_2$	Nesmeyanov, Kocheshkov, 1935
$(C_6H_5N_2)_2PbCl_6$	+ Zn	$\longrightarrow$	$(C_6H_5)_2PbCl_2$	Nesmeyanov, Kocheshcov, 1935
$C_6H_5N_2BF_4 + HgCl_2 + SnCl_2$		$\longrightarrow$	C_6H_5HgCl	Dunker *et al.*, 1936[22]
$C_6H_5N_2Cl$	+ M	$\longrightarrow$	$(C_6H_5)_{n-m}M_nCl_m$ M = Hg, Sn, Sb, S, Se, Te, As	Waters, 1937-1939[4]
$C_6H_5N_2BiCl_4$	+ Cu	$\longrightarrow$	$(C_6H_5)_3Bi$	Gilman, 1939
$C_6H_5N_2BiCl_4$	+ Bi	$\longrightarrow$	$(C_6H_5)_3Bi$	Nesmeyanov, Kocheshkov, 1940
$C_6H_5N_2SbCl_6$	+ Zn	$\longrightarrow$	$C_6H_5SbCl_2$; $(C_6H_5)_2SbCl$; $(C_6H_5)_3Sb$; $(C_6H_5)_3SbCl_2$	Nesmeyanov, Kocheshkov, 1944
$C_6H_5N_2BF_4$	+ Pb	$\longrightarrow$	$(C_6H_5)_4Pb$	Nesmeyanov, Kocheshkov, 1945
$C_6H_5N_2BF_4$	+ Tl	$\xrightarrow{Cl^-}$	$(C_6H_5)_2TlCl$	Nesmeyanov, Makarova, 1952[19]
$C_6H_5N_2BF_4 + SnCl_2$	+ Zn	$\longrightarrow$	$(C_6H_5)_2SnCl_2$; $(C_6H_5)_3SnCl$; $C_6H_5SnCl_3$	Nesmeyanov, Makarova, 1952[17]
$C_6H_5N_2BF_4$	+ MCl_3	$\xrightarrow{OH^-}$	$C_6H_5MO(OH)_2 + (C_6H_5)_2MO(OH)$ M = P, Sb, As	Doak, 1952-1954[23]

[3] M. Gomberg and W. E. Bachmann *J. Amer. Chem. Soc.* **46**, 2339 (1924); M. Gomberg and J. C. Pernert *J. Amer. Chem. Soc.* **48**, 1372 (1926); D. H. Hey and W. A. Waters *Chem. Rev.* **21**, 169 (1937); W. A. Waters *Chemistry of the free radicals* Oxford (1946).

[4] W. A. Waters *J. Chem. Soc.* 2007 (1937); 843, 1077 (1938); 864, 867 (1939).

with powdered metals,[4a] as well as a number of similar syntheses of organo-metallic compounds carried out at a later date (Table 3).[5]

This is the case also with diaryliodonium salts. Thus, diphenyliodonium chloride, under the action of a metal (mercury, selenium, tellurium), homolytically transfers its phenyl radical to form organo-metallic compounds.[6]

Whether the phenyl, transferred from ammonium or oxonium, would follow the alkyl ammonium and oxonium mechanism or the phenyl diazonium and iodonium one, could not be decided, tetra-aryl ammonium and triaryloxonium having been unknown.

In a series of investigations we have shown that it is possible to make diazonium and iodonium salts transfer their aromatic radical heterolytically. We have used this type of reaction to extend synthetic procedures as well as for obtaining new types of onium compounds such as diarylchloronium, diarylbromonium, and triaryloxonium.

To effect the heterolytic cleavage of phenyl from the iodonium and diazonium salts, it was necessary to decompose the salts of these onium cations with stable complex anions. In fact, it has been shown that phenyldiazonium and diphenyliodonium borofluorides do decompose heterolytically. In contrast to the corresponding chlorides, they do not form organo-mercuric compounds with metallic mercury. On the contrary the phenyl cation resulting from the decomposition of diphenyliodonium borofluoride[7] is fixed by a pair of free electrons of nitrogen, phosphorus, antimony, sulphur, and selenium in trimethylamine, pyridine, triphenylphosphine, triphenylarsine, triphenylstibine, diphenylsulphide, and diphenylselene, forming new onium borofluorides.

TABLE 4

$$(C_6H_5)_2\overset{+}{I}BF_4 + \begin{cases} :N(CH_3)_3 \longrightarrow C_6H_5N(CH_3)_3BF_4 \\ :NC_5H_5 \longrightarrow [C_6H_5NC_5H_5]BF_4 \\ :P(C_6H_5)_3 \longrightarrow (C_6H_5)_4PBF_4 \\ :As(C_6H_5)_3 \longrightarrow (C_6H_5)_4AsBF_4 \\ :Sb(C_6H_5)_3 \longrightarrow (C_6H_5)_4SbBF_4 \\ :S(C_6H_5)_2 \longrightarrow (C_6H_5)_3SBF_4 \\ :Se(C_6H_5)_2 \longrightarrow (C_6H_5)_3SeBF_4 \end{cases}$$

All these reactions give excellent yields. It should be noted that in none of the conditions investigated did the phenyl from diphenyliodonium chloride react with

[4a] A. N. Nesmeyanov *Zhur. Russ. khim. Obshch.* **61**, 1393 (1929); *Ber.* **62**, 1010 (1929); A. N. Nesmeyanov and E. I. Kahn *Zhur. Russ. khim. Obshch.*, **61**, 1407 (1929), *Ber.* **62**, 1018 (1929); A. N. Nesmeyanov and L. G. Makarova *Zhur. Obshchei. Khim.* **1**, 538 (1931); A. N. Nesmeyanov, N. Th. Glushnev, P. Th. Epifansky, and A. J. Flegontov *Zhur. Obshch. Khim.* **4**, 714, (1934); *Ber.* **67**, 130 (1934); A. N. Nesmeyanov *Uch. Zap. Mosk. Univ. ser. khim.* **3**, 291 (1934); A. N. Nesmeyanov and E. M. Toropova *Zhur. Obshchei Khim.* **4**, 664 (1934).

[5] A. N. Nesmeyanov, K. A. Kocheshkov, and V. A. Klimova *Zhur. Obshchei. Khim.* **6**, 167 (1936); *Ber.* **68**, 1877 (1935); K. A. Kocheshkov, A. N. Nesmeyanov, and N. K. Gipp *Zhur. Obshechei Khim.* **6**, 172 (1936); K. A. Kocheshkov and A. N. Nesmeyanov *Izvest. Akad. Nauk. Otdel. khim. nauk* 416 (1944); O. A. Reutov and O. A. Ptitsyna *Doklady Akad. Nauk.* **79**, 819 (1951); K. A. Kocheshkov, and A. N. Nesmeyanov *Zhur. Obshchei. Khim.* **6**, 144 (1936); T. K. Kozminskaya, M. M. Nadj and K. A. Kocheshkov *Zhur. Obshchei Khim.* **16**, 891, 897 (1946). Gilman and Svigoon *J. Amer. Chem. Soc.* **61**, 3586 (1939); Gilman and Yablunsky *J. Amer. Chem. Soc.* **63**, 949 (1941).

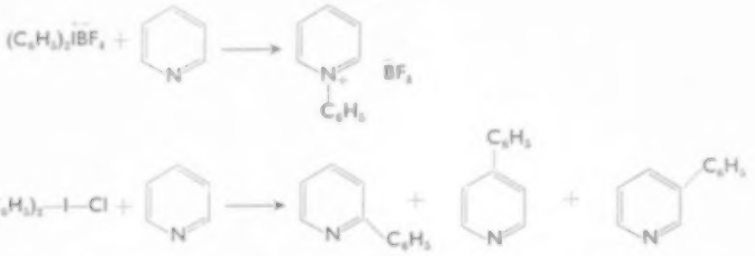
[6] R. B. Sandin, F. T. McClure and F. Irwin *J. Amer. Chem. Soc.* **61**, 2944 (1939).

[7] L. G. Makarova, and A. N. Nesmeyanov *Izvest. Akad. Nauk SSSR. Otdel. khim. nauk* 617 (1945).

triphenylarsine, triphenylstibine, diphenylsulphide, diphenylselene, but reacted with triphenylphosphine to form tetraphenyl-phosphonium in 40% yield.

The reaction with pyridine is the most definite indication of the ionic or radical decomposition. The phenyl cation formed by decomposing diphenyliodonium borofluoride results in the formation of the *N*-phenylpyridinium salt in 88% yield,[7] whilst the phenyl radical formed during the decomposition of diphenyliodonium and phenyldiazonium chlorides enters the pyridine nucleus[10a].

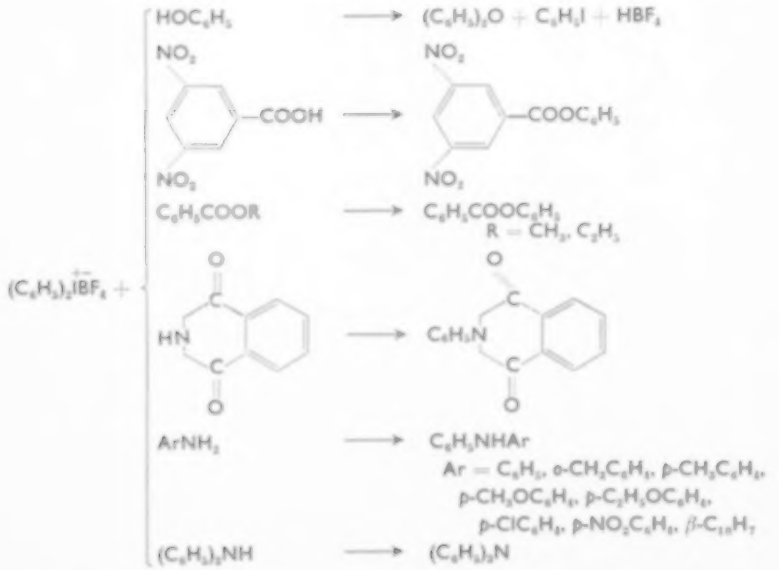
TABLE 5



The phenyl resulting from diphenyliodonium borofluoride also adds on the free pair of electrons of oxygen and nitrogen, thus phenylating the phenolic, carboxylic, and carbethoxylic oxygen and the nitrogen of amides[8] and amines[9]

Decomposition of diphenyliodonium borofluoride in phenol leads to diphenyloxide.

TABLE 6



[8] A. N. Nesmeyanov and L. G. Makarova *Uch. Zap. Mosk. Univ.* **132**, 109 (1950).
[9] L. G. Makarova *Izvest. Akad. Nauk SSSR, Otdel. khim. nauk* 741 (1951).
[10a] R. B. Sandin and R. K. Brown *J. Amer. Chem. Soc.* **69**, 2253 (1947).

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In capronic, benzoic, and 3,5-dinitrobenzoic acids it yields the corresponding phenyl esters. In the alkyl benzoate and phosphate, re-esterification takes place.

Decomposition of diphenyliodonium borofluoride in methyl and ethyl benzoate and in methyl, ethyl, *n*-propyl, and *n*-butyl phosphate results in the formation of the corresponding phenyl esters.

Decomposition of diphenyliodonium borofluoride in phthalimide leads to *N*-phenyl phthalimide, and decomposition in primary and secondary aromatic amines gives respectively secondary and tertiary amines.

Phenyl, resulting from diphenyliodonium borofluoride, does not add to triphenylamine or to triphenylbismuth.

The decomposition of aryldiazonium borofluorides was first observed to take place heterolytically in the benzene nucleus containing substituents.[10b] Phenyldiazonium borofluoride and other aryldiazonium borofluorides were decomposed in benzene derivatives containing meta-orienting substituents. Homolytic decomposition of aryldiazonium borofluorides should have led to the aryl radical entering the substituted benzene derivative mainly in ortho- and para-positions to any substituent. But if decomposition of aryldiazonium borofluorides takes place heterolytically, generating an aryl cation, then the latter should be affected by the usual orienting influence of the substituent in the benzene ring, and, being an electrophilic reagent, it has in this case to enter the benzene nucleus primarily in the meta-position to the meta-orienting group.

Decomposition of aryldiazonium borofluorides in a benzene derivative containing the following meta-orienting substituents, nitro group, quaternary ammonium nitrogen, carbalkoxy group, trifluoromethyl and acetyl groups, leads mainly to aryl occupying the meta-position to these meta-orientants.

In contrast to the decomposition of iodonium, the majority of diazonium decomposition reactions investigated resulted in poor yields of products formed by aryl cations entering the aromatic nucleus. In the benzene ring the meta-orienting influence of the substituents listed above is quite evident. Though, in some cases some ortho- and para-isomers were isolated, their amount was substantially less than that of meta-isomers. Low yields of benzene nucleus substitution products depend on the fact that the main reaction always proceeds following Schiemann with fluorobenzene formation and that in addition large amounts of the so-called "diazoresin" are formed.

Yet, on the whole, the general picture of the decomposition of diazonium borofluoride seems as convincing as that of diphenyliodonium borofluorides.

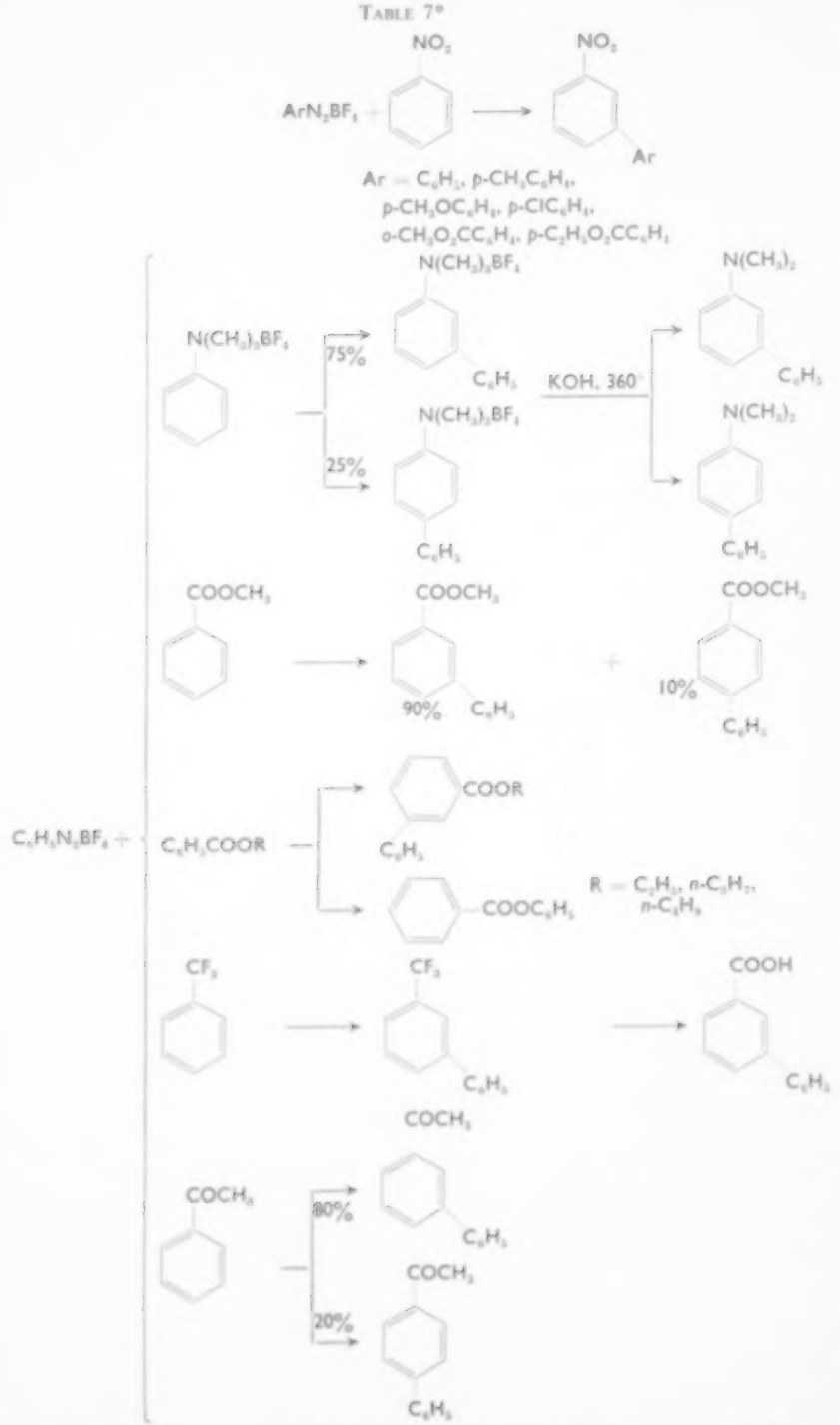
When the following aryldiazonium borofluorides are decomposed in nitrobenzene, aryl occupies the meta-position to the nitro group, the only biphenyl derivative isolated being in each case the respective meta-nitrobiaryl (Table 7).

The ultra-violet analysis of fractions containing nitrobiaryls showed the mixture to contain over 90% meta-derivatives.

Phenyldiazonium borofluoride decomposition in phenyl-trimethylammonium borofluoride has revealed (together with the predominance of products of meta-substitution) the formation of a smaller amount of a para-isomer (the reaction products were isolated as dimethylaminodiphenyls). The ratio of the meta-isomer to the para-isomer can be approximately calculated as 3 : 1.

[10b] A. N. Nesmeyanov and L. G. Makarova *Izvest. Akad. Nauk SSSR, Otdel. khim. nauk* 213 (1947).

TABLE 7*



* The figures represent the percentage ratio of isomers in the reaction product (but not the yield).

Phenyldiazonium borofluoride being decomposed in methyl, ethyl, *n*-propyl, *n*-butyl, benzoates, phenyl occupies the meta-position to the carbalkoxy group.

The reaction of phenyldiazonium borofluoride with ethyl, *n*-propyl, *n*-butyl benzoates leads after saponification to meta-diphenylcarboxylic acid.

Decomposition in methyl benzoate, besides phenyl occupying predominantly the meta-position, resulted also in some para-isomer formation. Phenyldiazonium borofluoride decomposition in the ethyl, *n*-propyl, *n*-butyl benzoates brought about, in addition, re-esterification and, just as in the case of diphenyliodonium, phenyl benzoate was formed, probably due to phenyl cation affecting the carbethoxy-group.

The phenyl cation from phenyldiazonium borofluoride also occupied the meta-position to the trifluoromethyl-group of benzotrifluoride. The only diphenylcarboxylic acid isolated after hydrolysis was the meta-acid.

Decomposition of phenyldiazonium borofluoride in acetophenone resulted in phenyl occupying essentially the meta-position to the acetyl group, a para-substitution product being also formed, though to a lesser extent.

We have isolated meta- and para-phenylacetophenones as such, and part of the meta- and para-phenylacetophenone mixture was subjected to the iodoformic reaction. The resulting mixture of meta- and para-diphenylcarboxylic acids was separated owing to the difference in solubilities of their sodium salts, the resulting acids being identified. By this procedure we have also determined the predominance of meta-isomer formation. Thus, even with a relatively weak meta-orientant, i.e. the acetyl group, the phenyl from the phenyldiazonium borofluoride occupied mainly the meta-position, showing in this case also a different behaviour from the phenyl derived from the homolytically decomposing phenyl source.

Decomposition of phenyldiazonium borofluoride in methyl and ethyl benzene

TABLE 8

$$C_6H_5N_2BF_4 + C_6H_5SO_2R \longrightarrow C_6H_5SO_2C_6H_5$$

$R = CH_3, C_2H_5$

$$C_6H_5N_2BF_4 + R\text{-}C{\equiv}N: \xrightarrow{H_2O} RCNHC_6H_5 \quad (O)$$

$R = C_6H_5, C_6H_5CH_2, o\text{-}CH_3C_6H_4,$

$p\text{-}CH_3C_6H_4, CH_3, C_2H_5, CH_2{=}CH$

$$(C_6H_5N_2)_2SiF_6 + RC{\equiv}N: \xrightarrow{H_2O} RCNHC_6H_5 \quad (O)$$

$R = C_6H_5, C_6H_5CH_2$

sulphonates did not give products resulting from phenyl entering the benzene ring of these esters. The phenyl attack was directed to the sulphalkoxy group and the only reaction product in both cases was phenyl benzenesulphonate in good yield.

Decomposition of phenyldiazonium borofluoride in nitrile medium leads to the addition of phenyl to nitrogen.[11] Hydrolysis of nitrilium borofluorides not isolated by us results in anilides of corresponding acids, the yield of benzanilide, starting for example from benzonitrile, being up to 40%. Similarly starting from benzylcyanide, phenylacetanilide was obtained. A similar reaction was carried out with ortho- and para-toluo-, propio-, and acrylonitriles.

The production of anilides by the reaction of diazo-compounds with nitriles is well known. Hanby and Waters,[12] when decomposing phenyldiazonium chloride in acetonitrile, observed the formation of a mixture consisting of benzene, acetophenone, and 10% acetanilide. Here the phenyl radical attacks alternatively the carbon or the nitrogen of the nitrile group or the α-attached hydrogen. In our case the phenyl cation attack took place on the nitrogen atom.

A number of similar results were obtained by us in decomposing aryldiazonium fluorosilicate.[13]

Without going into details, it may be mentioned that this excludes any specific role of boron trifluoride.

To prove the heterolytic mechanism of phenyldiazonium borofluoride decomposition, a reaction with compounds involving a double carbon-carbon bond was carried out.[8] It was supposed that the phenyl cation would add at the polar double bond, following Markovnikov rule and being acted upon by acrylic acid, should form different products from those obtained under the action of aryl radicals in the Meerwein-Koelsch reaction.

The decomposition of phenyldiazonium borofluoride in ethyl crotonate results in phenyl occupying the α-position to the ethoxycarbonyl group to yield (after saponification) methylatropic acid.[8] On the other hand, the decomposition in the same medium of phenyldiazonium chloride in the Meerwein-Koelsch reaction leads to phenyl occupying the β-position, to form α-chloro-β-phenylisobutyric acid.[14]

During the decomposition of phenyldiazonium borofluoride in methyl acrylate the phenyl attacks the α-carbon and the carboxylic oxygen. The main reaction products formed were atropic acid (after saponification) and phenyl acrylate.

The Meerwein-Koelsch reaction of phenyldiazonium chloride with methyl acrylate yields α-chloro-hydrocinnamic acid ester.[15]

Decomposition of phenyldiazonium borofluoride in methyl-methacrylate also results in different products from those formed with phenyldiazonium chloride,[16] α-methylcinnamic acid being formed after hydrolysis in the latter case.

As a result of this reaction, benzyl-acrylic acid was obtained (after saponification) and 5-hydroxy-2-methyl-hydrindenone, a product of further conversion of the phenyl-methacrylate.

[11] L. G. Makarova and A. N. Nesmeyanov *Izvest. Akad. Nauk. SSSR, Otdel. khim. nauk* 1019 (1954).
[12] W. E. Hanby and W. A. Waters *J. Chem. Soc.* 1792, (1939).
[13] L. G. Makarova and M. K. Matveeva *Izvest. Akad. Nauk. SSSR, Otdel. khim. nauk* 435 (1956).
[14] C. F. Koelsch and V. Boekelheide *J. Amer. Chem. Soc.* **66**, 412 (1944).
[15] C. F. Koelsch *J. Amer. Chem. Soc.* **65**, 57 (1943).
[16] P. L'Ecuyer and Ch. A. Olivier *Canad. J. Research* **28**, 648 (1950); M. Krischnamurti and K. B. Lal Mathur *J. Indian. Chem. Soc.* **28**, 507 (1951).

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TABLE 9

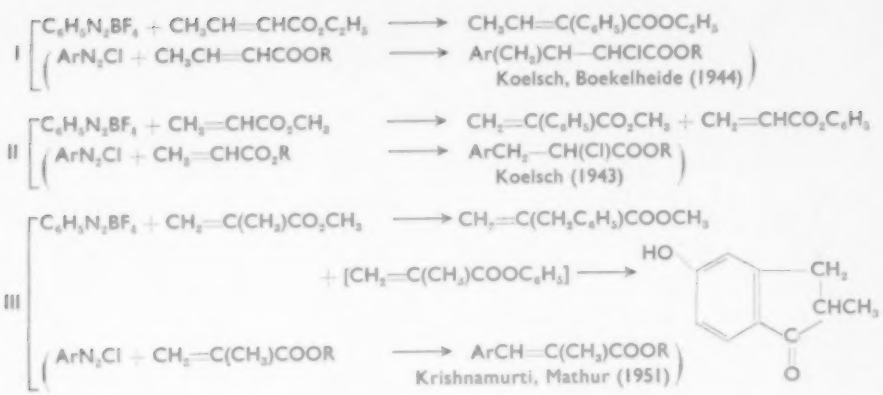

Table 3 records the comparative data of the synthesis of organo-metallic (and organo-element) compounds through double diazonium salts and the homolytic synthesis of the same compounds obtained from diazonium chloride and a metal. In cases where the double salt procedure with the same metal results in a poor yield (as, for example, in the synthesis of organo-lead and tin compounds) and the direct action of diazonium halide on a metal also gives little or no result, diazonium borofluorides give good results.

Thus, as has been shown, it is possible to obtain a 40% yield of organo-tin compounds[17] (reaction N 12), up to 30% of organo-lead compounds[18] (reaction N 10) as well as organo-thallium compounds[19] (reaction N 11), formerly not available through diazo-compounds.

The table suggests two parallels. First, a parallel between the direct attack of the decomposing diazonium halides on the free metal in Waters[20, 12] and McClure[21] reactions and our reactions of organo-metallic syntheses through double diazonium salts. It is concluded that in both cases homolytic reactions of identical mechanism are involved. Secondly, there is a parallel between diazonium borofluoride syntheses and all our syntheses through onium borofluoride compounds mentioned above. This analogy seems in both cases to demand a heterolytic mechanism.[22]

One can, however, hardly imagine a heterolytic mechanism of synthesis of an organo-metallic compound by diazonium borofluoride acting on a free metal. If it were homolytic, why should diazonium borofluoride prove successful in cases where its chloride failed? It is impossible at present to come to any conclusions. The following correlations can be of some help in elucidating this point.

Iodonium and diazonium borofluorides behave essentially in a similar way. But there is a difference in their behaviour in reactions where both borofluorides are acted on by a base, as, for example, by pyridine.

It has already been mentioned above that iodonium borofluoride as a result of an

[17] A. N. Nesmeyanov and L. G. Makarova *Doklady Akad. Nauk SSSR* **87**, 421 (1952).
[18] A. N. Nesmeyanov and L. G. Makarova *Izvest. Akad. Nauk SSSR, Otdel. khim. nauk* 380 (1954).
[19] A. N. Nesmeyanov and L. G. Makarova *Doklady Akad. Nauk SSSR* **87**, 417 (1952).
[20] W. A. Waters *J. Chem. Soc.* **1937**, 113; 2007, **1938**, 1077; **1939**, 864; F. B. Makin and W. A. Waters *J. Chem. Soc.*, **1938**, 843.
[21] R. E. McClure and A. Lowy *J. Amer. Chem. Soc.* **53**, 319 (1931).
[22] O. A. Reutov *Tetrahedron* **1**, 67 (1957).

obviously heterolytic decomposition up to 90%, forms with pyridine *N*-phenylpyridinium borofluoride. On the other hand, phenyldiazonium borofluoride behaves with pyridine like phenyldiazonium or diphenyliodonium chloride forming a mixture of α- and γ-phenylpyridines.

For obvious reasons we are dealing with a homolytic reaction. Pyridine like the hydroxyl ion appears first to convert the diazonium cation into a diazo-compound, which is then homolytically decomposed. Since this conversion, like that of diazonium hydroxide into diazo-hydrate, is impossible for the diphenyliodonium cation, diphenyliodonium borofluoride in all cases decomposes heterolytically.

For this reason, in contrast to diphenyliodonium chloride, it does not give with metallic mercury any organo-mercuric compound. In the Dunker reaction,[23] phenyldiazonium borofluoride forms phenylmercury chloride similar to the formation of the latter from phenyldiazonium chloride and mercury in the McClure reaction.[21] Thus we are led to assume that free metal acts on the diazonium cation as electron-releasing reagent, similar to a base, causing it to decompose homolytically with a previous conversion into a diazo-form.

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This assumption is supported by the decomposition of aryldiazonium borofluoride in nitrobenzene in the presence of large amounts of powdered copper, the process without copper resulting, as already stated above, in an almost pure meta-nitrobiaryl. Copper induces the process to run along the homolytic mechanism, as seen by exclusive formation of ortho- and para-nitrobiaryl. A similar difference is to be observed in the results of decomposition of phenyldiazonium borofluoride in ethyl benzoate in the presence or absence of powdered copper. In the latter case the decomposition seems to run heterolytically, as it leads to re-esterification, yielding phenyl benzoate, and to formation of metaphenyl benzoate. With copper, due to homolysis, the phenyl radical attacks the aromatic nucleus, yielding ethyl paraphenylbenzoate as the main reaction product.

As a new result of heterolysis of aryldiazonium borofluoride, one may mention the transfer of the phenyl cation to the free electron pair of bromine, chlorine, and oxygen in bromobenzene, chlorobenzene, and diphenyloxide respectively, to yield previously unknown cations of diphenylbromonium,[24] diphenylchloronium,[25] and triphenyloxonium.[26] Gradually introducing phenyldiazonium borofluoride into an excess of halogen benzene at 60° and mixing until the diazo-compound is completely decomposed, one obtains in a 0·55% of theory yield diphenyl halogenonium borofluoride which is extracted by water. From the water extract it is precipitated with chloroplatinic acid or with sodium tetraphenylborate and in the case of diphenylbromonium cation with an iodine ion as well. The reaction being carried out in the same way, by introducing the acetone solution of phenyldiazonium borofluoride into the halogenbenzene at about 80°, it is possible to raise the yield up to 6% of theory.

Diphenylbromonium compounds are typical salts with a colourless cation, more soluble than the corresponding diphenyliodonium salts. Chloride, bromide, nitrate, nitrite, sulphate, acetate, borofluoride, and a number of others are soluble in water.

[23] M. F. B. Dunker, E. B. Starkey, and G. L. Jenkins *J. Amer. Chem. Soc.* **58**, 2308 (1936); M. F. B. Dunker and E. B. Starkey *J. Amer. Chem. Soc.* **61**, 3005 (1939).
[24] A. N. Nesmeyanov, T. P. Tolstaya, and L. S. Isaeva *Doklady Akad. Nauk SSSR* **104**, 872 (1955).
[25] A. N. Nesmeyanov and T. P. Tolstaya *Doklady Akad. Nauk SSSR* **105**, 94 (1955).
[26] A. N. Nesmeyanov, N. V. Kruglova, R. B. Materikova, and T. P. T. Tolstaya *Zhur. Obshchei Khim.* **26**, 2211 (1956).

TABLE 10

			F. (dec.)
$C_6H_5\dot{N}_2\bar{B}F_4$	⟶	$(C_6H_5)_2\dot{B}r\bar{B}F_4 + N_2$	120–121°
C_6H_5Br		$(C_6H_5)_2\dot{B}r\bar{B}r$	82–83°
		$(C_6H_5)_2\dot{B}r\bar{I}$	81–82°
		$(C_6H_5)_2\dot{B}r\bar{H}gI_3$	108–109°
		$[(C_6H_5)_2\dot{B}r]_2\bar{P}tCl_6$	160°
		$(C_6H_5)_2\dot{B}r\bar{B}(C_6H_5)_4$	165°
$p\text{-}CH_3C_6H_4\dot{N}_2\bar{B}F_4$	⟶	$(p\text{-}CH_3C_6H_4)(C_6H_5)\dot{B}r\bar{B}F_4$	78°
C_6H_5Br		$(p\text{-}CH_3C_6H_4)(C_6H_5)\dot{B}r\bar{I}$	81–82°
		$(p\text{-}CH_3C_6H_4)(C_6H_5)\dot{B}r\bar{H}gI_3$	110–111°
		$[(p\text{-}CH_3C_6H_4)(C_6H_5)\dot{B}r]_2\bar{P}tCl_6$	152°
		$(p\text{-}CH_3C_6H_4)(C_6H_5)\dot{B}r\bar{B}(C_6H_5)_4$	~135°
$o\text{-}CH_3C_6H_4\dot{N}_2\bar{B}F_4$	⟶	$(o\text{-}CH_3C_6H_4)(C_6H_5)\dot{B}r\bar{B}F_4$	112–113°
C_6H_5Br		$(o\text{-}CH_3C_6H_4)(C_6H_5)\dot{B}r\bar{I}$	65–66°
		$(o\text{-}CH_3C_6H_4)(C_6H_5)\dot{B}r\bar{H}gI_3$	92°
		$[(o\text{-}CH_3C_6H_4)(C_6H_5)\dot{B}r]_2\bar{P}tCl_6$	142°
$2,4\text{-}(CH_3)_2C_6H_3\dot{N}_2\bar{B}F_4$	⟶	$[2,4\text{-}(CH_3)_2C_6H_3](C_6H_5)\dot{B}r\bar{B}F_4$	104–105°
C_6H_5Br		$[2,4\text{-}(CH_3)_2C_6H_3](C_6H_5)\dot{B}r\bar{I}$	66°
$p\text{-}ClC_6H_4\dot{N}_2\bar{B}F_4$	⟶	$(p\text{-}ClC_6H_4)(C_6H_5)\dot{B}r\bar{H}gI_3$	97–98°
C_6H_5Br		$[(p\text{-}ClC_6H_4)(C_6H_5)\dot{B}r]_2\bar{P}tCl_6$	137–138°
$p\text{-}C_2H_5OOCC_6H_4\dot{N}_2\bar{B}F_4$	⟶	$[(p\text{-}C_2H_5OOCC_6H_4)(C_6H_5)\dot{B}r]_2\bar{H}gI_2$	79°
C_6H_5Br		$[(p\text{-}C_2H_5OOCC_6H_4)(C_6H_5)\dot{B}r]_2\bar{P}tCl_6$	127°
		$(p\text{-}C_2H_5OOCC_6H_4)(C_6H_5)\dot{B}r\bar{B}(C_6H_5)_4$	142–144°
$\beta\text{-}C_{10}H_7\dot{N}_2\bar{B}F_4$	⟶	$(\beta\text{-}C_{10}H_7)(C_6H_5)\dot{B}r\bar{I}$	77°
C_6H_5Br			

Iodide, chloroplatinate, and tetraphenylborate are sparingly soluble. The two latter salts are stable at room temperature. The chloroplatinate decomposes at 159·5° and tetraphenylborate at 164–165°. Iodide is not stable, decomposing in 1–2 days into a mixture of bromo- and iodobenzene. It decomposes at 81–82°. Diphenylchloronium salts are considerably less stable. The action of an iodine ion on borofluoride solution leads to the formation of diphenylchloronium iodide, which decomposes at 56–57°. Chloroplatinate decomposes at 142·5–143°, tetraphenylborate at 160–161°.

In the Tables 10 and 11, are listed all diarylbromonium and diarylchloronium salts which we have obtained and are at present investigating.

Thus, by introducing the acetone solution of diazonium borofluoride, into diphenyl oxide at 80–90°, after half an hour's heating at the same temperature triphenyloxonium borofluoride is obtained from the water extract, after removing acetone and cooling. It is an extremely stable compound, decomposing at 226°.

TABLE 11

			F. (dec.)
$C_6H_5\overset{+}{N}_2\overset{-}{BF_4}$	⟶	$(C_6H_5)_2\overset{+}{C}l\overset{-}{BF_4}$ + N_2	109·5–110°
		$(C_6H_5)_2\overset{+}{C}l\,\overset{-}{I}$	56–57°
C_6H_5Cl		$(C_6H_5)_2\overset{+}{C}l\overset{-}{B}(C_6H_5)_4$	161°
		$[(C_6H_5)_2\overset{+}{C}l]_2\overset{--}{PtCl_6}$	143°
p-$CH_3C_6H_4\overset{+}{N}_2\overset{-}{BF_4}$	⟶	$(p\text{-}CH_3C_6H_4)(C_6H_5)\overset{+}{C}l\overset{-}{HgI_3}$	93–94°
C_6H_5Cl		$[(p\text{-}CH_3C_6H_4)(C_6H_5)\overset{+}{C}l]_2\overset{--}{PtCl_6}$	139°
		$(p\text{-}CH_3C_6H_4)(C_6H_5)\overset{+}{C}l\overset{-}{B}(C_6H_5)_4$	127°
o-$CH_3C_6H_4\overset{+}{N}_2\overset{-}{BF_4}$	⟶	$(o\text{-}CH_3C_6H_4)(C_6H_5)\overset{+}{C}l\overset{-}{HgI_3}$	64°
C_6H_5Cl		$[(o\text{-}CH_3C_6H_4)(C_6H_5)\overset{+}{C}l]_2\overset{--}{PtCl_6}$	123–124°
2.4-$(CH_3)_2C_6H_3\overset{+}{N}_2\overset{-}{BF_4}$	⟶	$[2.4\text{-}(CH_3)_2C_6H_3](C_6H_5)\overset{+}{C}l\overset{-}{HgI_3}$	83°
C_6H_5Cl		$[[2.4\text{-}(CH_3)_2C_6H_3](C_6H_5)\overset{+}{C}l]_2\overset{--}{PtCl_6}$	144°
p-$C_2H_5OOCC_6H_4\overset{+}{N}_2\overset{-}{BF_4}$	⟶	$[(p\text{-}C_2H_5OOCC_6H_4)(C_6H_5)\overset{+}{C}l]_2\overset{--}{HgI_4}$	58·5–60°
C_6H_5Cl		$[(p\text{-}C_2H_5OOCC_6H_4)(C_6H_5)\overset{+}{C}l]_2\overset{--}{PtCl_6}$	106·5–108°
		$(p\text{-}C_2H_5OOCC_6H_4)(C_6H_5)\overset{+}{C}l\overset{-}{B}(C_6H_5)_4$	121–124°
$C_6H_5\overset{+}{N}_2\overset{-}{BF_4}$	⟶	$(p\text{-}ClC_6H_4)(C_6H_5)\overset{+}{C}l\overset{-}{HgI_3}$	84°
p-ClC_6H_4Cl		$[(p\text{-}ClC_6H_4)(C_6H_5)\overset{+}{C}l]_2\overset{--}{PtCl_6}$	119–120°

In Table 12 are listed some representatives of this previously unknown type of tertiary aromatic oxonium salts which we have obtained.

TABLE 12

			F. (dec.)
$C_6H_5\overset{+}{N}_2\overset{-}{BF_4}$ ⟶	$(C_6H_5)_3\overset{+}{O}\overset{-}{BF_4}$	226°
$(C_6H_5)_2O$		$(C_6H_5)_3\overset{+}{O}\overset{-}{Br}$	182–182·5°
		$(C_6H_5)_3\overset{+}{O}\overset{-}{I}$	177–178°
		$(C_6H_5)_3\overset{+}{O}\overset{-}{HgI_3}$	156–157°
		$(C_6H_5)_3\overset{+}{O}\overset{-}{B}(C_6H_5)_4$	~165°
		$[(C_6H_5)_2\overset{+}{O}]_2\overset{--}{PtCl_6}$	184–185°
		$[(C_6H_5)_2\overset{+}{O}]_2\overset{--}{Cr_2O_7}$	177–178° darkened
		$(C_6H_5)_2\overset{+}{O}C_6H_2(NO_2)_3\overset{-}{O}$	155–157°

It is rather striking that decomposition of phenyl-diazonium borofluoride into iodobenzene leaves no traces in diphenyliodonium salt. On the other hand, the homolytic decomposition of phenyldiazoacetate in iodobenzene gives a small amount of diphenyliodonium salt. In contrast, decomposition of diazophenyl acetate in chloro- and bromobenzene does not lead to any diphenylhalogenonium salts. Thus, the path to diarylchloronium and diarylbromonium consists in the heterolytic transfer of the phenyl cation to the aromatic halogen.

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Finally, it may be recalled that the first to discover bromonium and chloronium salts were Sandin and Hey,[27] who in 1952 described the reaction leading to the formation of cyclic *o,o'*-diphenylene halogenonium in aqueous solution, a reaction similar to the reaction of Mascarelli,[28] which had enabled him to produce diphenylene iodonium.

Up to the present we have studied to some extent only the reactions of diphenylchloronium and diphenylbromonium salts. These compounds, less stable than iodonium salts, especially as far as diphenylchloronium salts are concerned, behave, on the whole, very similarly to diphenyliodonium salts. Their borofluorides in any medium, and their iodides in aqueous medium phenylate amines, converting for example, diethylamine into diethylaniline, pyridine into *N*-phenyl-pyridinium borofluoride. Sodium nitrite is phenylated into nitrobenzene, potassium cyanide into benzonitrile, etc. Diphenylbromonium and diphenylchloronium borofluorides do not react with metallic mercury. On the other hand, the iodides of these cations form with metallic mercury in alcoholic-medium phenylmercuryiodide, this time due to a homolytic reaction. It is difficult to explain the homolytic reaction otherwise than due to the formation of a covalent form of diphenylhalogenonium iodide, the bromine or chlorine octette being thus extended to a decette.

Thus, new halogenonium salts, just as iodonium ones, enable one to arylate arbitrarily according to either heterolytic or homolytic mechanism, these reactions taking place in milder conditions, than those of iodonium salts. If it were possible to find conditions for producing diarylchloronium and diarylbromonium salts in a higher yield, these salts would undoubtedly serve as excellent arylating reagents.[29]

[27] R. B. Sandin and A. S. Hey *J. Amer. Chem. Soc.* **74**, 274 (1952).
[28] Z. Mascarelli *Atti Acad. Lincei* (5) **16**, II, 582 (1907).
[29] G. O. Doak and L. D. Freedman *J. Amer. Chem. Soc.* **73**, 5656, 5658 (1957); **74**, 830 (1952).

Tetrahedron, 1957, Vol. 1, pp. 158–168. Pergamon Press Ltd., London

STEREOCHEMISTRY OF ELECTROPHILIC AND HOMOLYTIC SUBSTITUTION AT THE OLEFINIC CARBON

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VOL.
1
1957

(*Received* 10 *January* 1957)

STEREOCHEMICAL regularities of the exchange reactions at the tetrahedric carbon atom have been under investigation since the time of the classical works of Walden, this type of substitution having been dealt with in numerous investigations. Recently there have also appeared investigations devoted to the electrophilic exchange at the saturated carbon atom, including those by one of us and O. A. Reutov.[1] Until our work dealing with the stereochemistry of the exchange at the olefinic carbon appeared there was almost no information available, neither were there investigations relating to the electrophilic substitution. From the works of Autenrieth[2] one can deduce that in the nucleophilic substitutions *cis* and *trans* configurations of the olefinic carbon are sometimes retained and sometimes inverted. Indeed, the reaction of sodium phenolate with β-chlorocrotonic and β-chloro*iso*crotonic acid gives the same phenoxycrotonic acid. Similar stereochemical changes are observed with sodium ethylate as well as in the Meyer reaction of the above-mentioned acids with sodium arsenite.

Chlorocrotonic and chloro*iso*crotonic acids react with sodium phenyl, ethyl, and benzyl mercaptides, each yielding its isomer of β-aralkylthiocrotonic acid, whether converted or not being unknown. We have similar information concerning the reaction of the chlorocrotonic acids with sodium phenyl-sulphinate.[2]

We have carried out a number of investigations, the first published in 1948,[3] dealing with the stereochemistry of electrophilic and homolytic exchange at the olefinic carbon atom.

The main results of our investigations are shown in Table 1. All exchange reactions of the metallic atom in β-chlorovinyl organo-metallic compounds* in this Table readily take place under mild conditions at room temperature to 80°.

* These reactions have been investigated partly by present-day writers, partly by one of the writers of this paper and by R. Kh. Freidlina and A. K. Kochetkov.[3a]

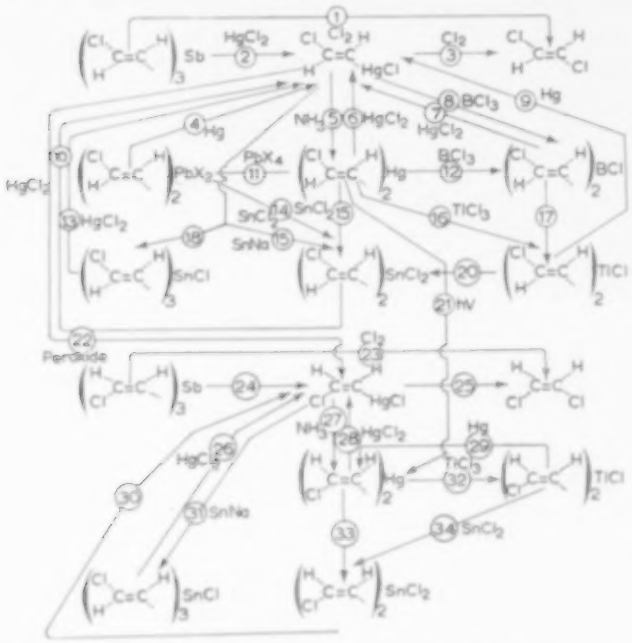
[1] A. N. Nesmeyanov, A. O. Reutov, and S. S. Poddubnaya *Doklady Akad. Nauk SSSR* **88,** 479 (1953); A. N. Nesmeyanov, A. O. Reutov, and S. S. Poddubnaya *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* 649 (1953); A. O. Reutov and A. N. Nesmeyanov *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* 655 (1953); A. N. Nesmeyanov, A. O. Reutov, and S. S. Poddubnaya *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* 850 (1953); A. O. Reutov and M. A. Besprozvanny *Doklady Akad. Nauk SSSR* **80,** 765 (1951).

[2] W. Autenrieth *Lieb. Ann.* **254,** 222 (1889); **259,** 332 (1890); R. Friedrich *Lieb. Ann.* **219,** 322 (1883); H. J. Backer and R. P. van Oosten *Rec. Trav. Chim. Pays Bas* **59,** 41 (1940).

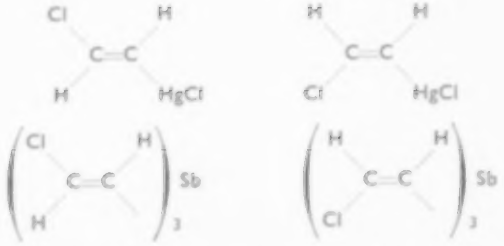
[3] A. N. Nesmeyanov and A. E. Borisov *Doklady Akad. Nauk* **60,** 67 (1948).

[3a] A. N. Nesmeyanov, R. Kh. Freidlina, and A. K. Kochetkov *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* **127,** 445 (1948).

TABLE 1



The majority of these reactions are undoubtedly those of electrophilic substitution, the metallic atom shifting and combining without the electron pair. In a number of cases (action of a metal, e.g. mercury, tin-sodium alloy, stannous chloride) it is undoubtedly a homolytic exchange. The starting compounds used in all these conversions were four substances, produced independently of each other from acetylene and mercury chloride[4] and respectively from acetylene and antimony pentachloride.[5]



By the action of ammonia each mercury chlorovinyl was completely converted into its corresponding mercury *bis*-chlorovinyl.

The correct assignment of the configuration of each of the four starting organomercuric chlorovinyl derivatives is of extreme importance in dealing with the problems under consideration. The configurations of β-chlorovinylmercury chlorides

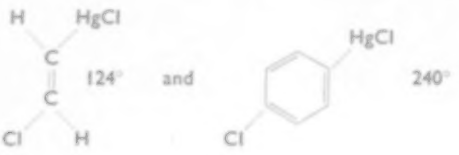
[4] A. N. Nesmeyanov and R. Kh. Freidlina *Doklady Akad. Nauk SSSR* **26**, 59 (1940); A. N. Nesmeyanov and A. E. Borisov *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* 289 (1947); R. Kh. Freidlina and O. V. Nogina *Izvest. Akad. Nauk. SSSR, Otdel. khim. Nauk* 105 (1947).

[5] A. N. Nesmeyanov and A. E. Borisov *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* 251 (1945); A. N. Nesmeyanov *Izvest. Akad. Nauk SSSR, Otdel khim. Nauk* 239 (1945).

are clear from the comparison of their dipole moments[6] (i.e. the vector sums of two dipole moments of $\overrightarrow{Hg—Cl}$ and $\overrightarrow{C—Cl}$ bonds, the larger one being 2·76*D* for the substance to which we assigned the *cis* configuration and the smaller 1·64*D* for the trans compound).

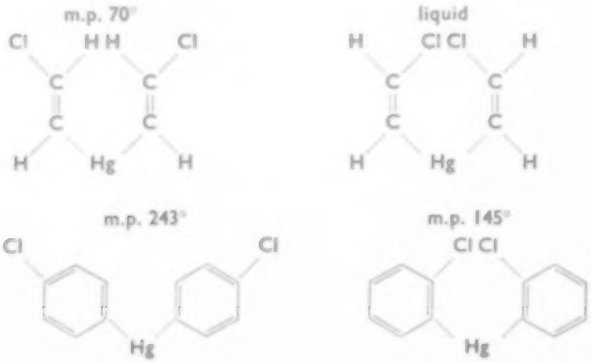
The *trans* configuration of *β*-chlorovinylmercury chloride, with a high melting-point, as well as that of its corresponding chlorovinylmercury bromide, has also been unambiguously determined by X-ray analysis, carried out at our request by A. I. Kitaigorodsky.[7]

Finally, the assignment of configurations is in agreement with the Werner's rule, as indicated by higher melting-points and lower solubilities of the compounds:



as compared with

The configurations of the two mercury dichlorovinyl derivatives follow from Werner's rule,



as well as from the Raman spectra of the *trans*-isomer. This assignment of the configurations is definitely proved by partial chlorination of both compounds[8] (in CCl_4 solution). Thereby

$$(ClCH{=}CH)_2Hg + Cl_2 \longrightarrow ClCH{=}CHHgCl + ClCH{=}CHCl$$

[6] A. N. Nesmeyanov, R. Kh. Freidlina, and A. E. Borisov *Izvest. Akad. Nauk. SSSR, Otdel. khim. Nauk* 137 (1945).
[7] A. I. Kitaigorodsky *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* 170 (1945); 259 (1947).
[8] A. N. Nesmeyanov, A. E. Borisov, and A. I. Guskova *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* 639 (1945).

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In the organo-metallic compound obtained, the ethylenic carbon atoms remain unaffected by the reaction, the chlorovinyl groups thereby retaining their configuration. This reaction is therefore suitable for establishing the stereochemical similarity between dichlorvinyl and monochlorovinyl organo-mercuric compounds. As a result of this reaction, the solid mercury di-β-chlorovinyl forms, pure high-melting *trans*-β-chlorovinylmercury chloride almost quantitatively, and the liquid di-β-chlorovinylmercury yields, also quantitatively, pure *cis*-β-chlorovinylmercury chloride. The pronounced difference in the solubilities of the latter and former chlorides in petroleum ether would have revealed the presence of any isomeric admixture. The assignment of the configurations independently of antimony chlorovinyl compounds obtained from acetylene has been based on the following considerations:

In the readily proceeding exchange-reactions of mercury chloride, the solid (m.p. 48–49°) trichlorovinylstibine immediately forms pure *trans*-(I)-chlorovinylmercury chloride and, correspondingly, the liquid trichlorovinylstibine yields *cis*-(II)-chlorovinylmercury chloride without any stereoisomer admixture.

I $(ClCH{=}CH)_3SbCl_2$ (m.p. 93–94°) $\longrightarrow$ $(ClCH{=}CH)_3Sb$ (m.p. 48–49°) $\xrightarrow{HgCl_2}$ $ClCH{=}CHHgCl$ (m.p. 124°)

II $(ClCH{=}CH)_3SbCl_2$ (m.p. 61–62°) $\longrightarrow$ $(ClCH{=}CH)_3Sb$ (liquid) $\xrightarrow{HgCl_2}$ $ClCH{=}CHHgCl$ (m.p. 79°)

It therefore follows that the initial antimony compound could not in the two cases (I, II) have been of a mixed form (*cis-cis-trans* or *cis-trans-trans*).

The configuration of the solid trichlorovinylstibine as *trans-trans-trans* compound follows from the detailed X-ray pattern analysis, made by Kitaigorodsky and Struchkov, on tri-β-chlorovinyldichlorostibine, which, on reduction of an antimony atom, yields solid trichlorvinylstibine. The configuration of chlorovinyl groups does not seem to be thereby affected.

According to Raman spectra analysis carried out by M. I. Batuyev at our request, only the liquid stereoisomer of trichlorovinylstibine displays in the Raman spectra two intensive bands in the 400–600 $^{-1}$ cm range, which distinguishes the *cis* compounds of the RCH=CHR′ type from their *trans*-isomers (frequencies, 425 cm^{-1} (intensity, 10) and 581 cm^{-1} (intensity, 7). Analysis of *cis-cis*-dichlorvinylmercury revealed frequencies of 420 cm^{-1} (intensity, 10) and 591 cm^{-1} (intensity, 8). The spectra of trichlorovinylstibine with m.p. 48–49° revealed no bands in this range. These criteria do not hold for *trans*-di-β-chlorovinylmercury, as irradiation converts it into the *cis* form.

As far as the two di-β-chlorovinyldichlorostannanes are concerned, they are pure forms and not *cis-trans* modifications, each of them yielding with mercuric chloride only one stereoisomer of chlorovinylmercury chloride.

The constants of the stereoisomeric dichloroethylenes are well known—(*trans* compound: b.p. 48·3°, $d_4^{15°} = 1{\cdot}2650$, $d_4^{25°} = 1{\cdot}2489$, $n_D^{18} = 1{\cdot}4466$; *cis* isomer: b.p. 59·8°, $d_4^{15°} = 1{\cdot}2896$, $n_D^{17} = 1{\cdot}44992$).

Chlorination of *trans*-chlorovinylmercury chloride immediately led to pure *trans*-dichloroethylene (m.p. 47·5°/741 mm, $d_4^{18°} = 1{\cdot}2574$, $n_D^{18°} = 1{\cdot}4468$).

Chorination of the mercuric *cis*-isomer also gave pure *cis*-dichloroethylene

(b.p. 58–59°, $d_4^{20°} = 1{\cdot}2819$, $n_D^{17°} = 1{\cdot}4493$, $n_D^{20} = 1{\cdot}4475$), rectification being carried out on a column with 20 theoretical plate efficiency. Thus, apart from $(ClCH{=}CH)_2PbX_2$(X=Chlorine, CH_3COO), $(ClCH{=}CH)_2TlCl$ compounds and both isomers $(ClCH{=}CH)_2SnCl_2$, configurations of all compounds listed in the table leave no room for doubt.

The following argument proves that of lead, thallium, and crystalline tin chlorovinyl compounds produced from *trans*-dichlorovinylmercury are *trans* forms and that the liquid-tin and thallium chlorovinyl compounds obtained from *cis*-dichlorovinylmercury are *cis* forms. Starting from *trans*-chlorovinylmercury chloride, it is possible to effect cyclic reactions, involving 2, 3, or 4 cycles and always reverting to the same parent *trans*-β-chlorovinylmercury chloride (5, 6), (5,11,4), (5, 16, 9), (5, 15, 10), (5, 11, 14, 10), (5, 16, 20, 10). The di-β-chlorovinyldichlorostannane produced in numerous conversions by different routes with a different number of steps (reactions N 15, 14, 20) is also always the same, melting at 77·5–78·5°. It is inconceivable that in all these different cycles, conversions of the trans configuration of the chlorovinyl radical into *cis* configuration would proceed just the necessary number of times for it to regain its original form. We have named this method as one of odd and even cycles. Starting from *cis*-chlorovinylmercury chloride, the reactions N 27 and N 33 result in liquid di-β-chlorovinyldichlorostannane, which is again converted N 30 into *cis*-chlorovinylmercury chloride, under the action of mercuric chloride.

Thus, the group of compounds obtained by conversions of tri-*trans*-β-chlorovinylstibine and *trans*-β-chlorovinylmercury chloride, on the one hand, and that of compounds obtained from the *cis*-isomers of these compounds on the other, are independent groups interconnected only by means of conversion of di-*trans*-β-chlorovinylmercury into the *cis*-isomer under the effect of irradiation and a similar conversion of *trans*-dichlorovinylstannane into the *cis*-isomer (omitted in the Table).

We have found[9] also that *trans*-chlorovinylmercury chloride is converted into its *cis*-isomer—poorer in energy[10]—when the solution is heated with benzoyl, acetyl, or with sodium peroxides.

Thus, all exchange reactions listed in the table proceed with strict retention of the configuration of the chlorovinyl group when transferred from one atom to another.

It follows therefore, that electrophilic and homolytic substitutions at the olefinic carbon atom take place without any change of configuration.

This assertion, made by the present authors in a paper in 1948,[3] has been further substantiated in our more recent investigations.[11]

In Table 2 are presented three isomeric products of mercury acetate in reaction with dimethylacetylene.

Two of them are stereoisomeric, as shown for instance by ozonolysis (only acetic acid being formed) and regeneration of dimethylacetylene by the action of potassium iodide. One of the isomers (presumably) *trans*-2 acetoxy-3-chloromercury-butene-2, m.p. 140°, is converted by ammonia into a symmetrical compound of the R_2Hg type, m.p. 113–114°, the latter being converted by the action of thallium trichloride into an organic substance of the R_2TlCl type. Each of these conversions can be

[9] A. N. Nesmeyanov, A. E. Borisov, and A. D. Vilchevskaya *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* 578 (1949).
[10] E. A. Shilov and I. V. Smirnov-Zamkov, *Dopovidi Akad. Nauk Ukr.SSR* 87-92 (1951).
[11] A. E. Borisov, V. D. Vilchevskaya, and A. N. Nesmeyanov, *Doklady Akad. Nauk SSSR*, **90**, 383 (1953); *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* 1008 (1954).

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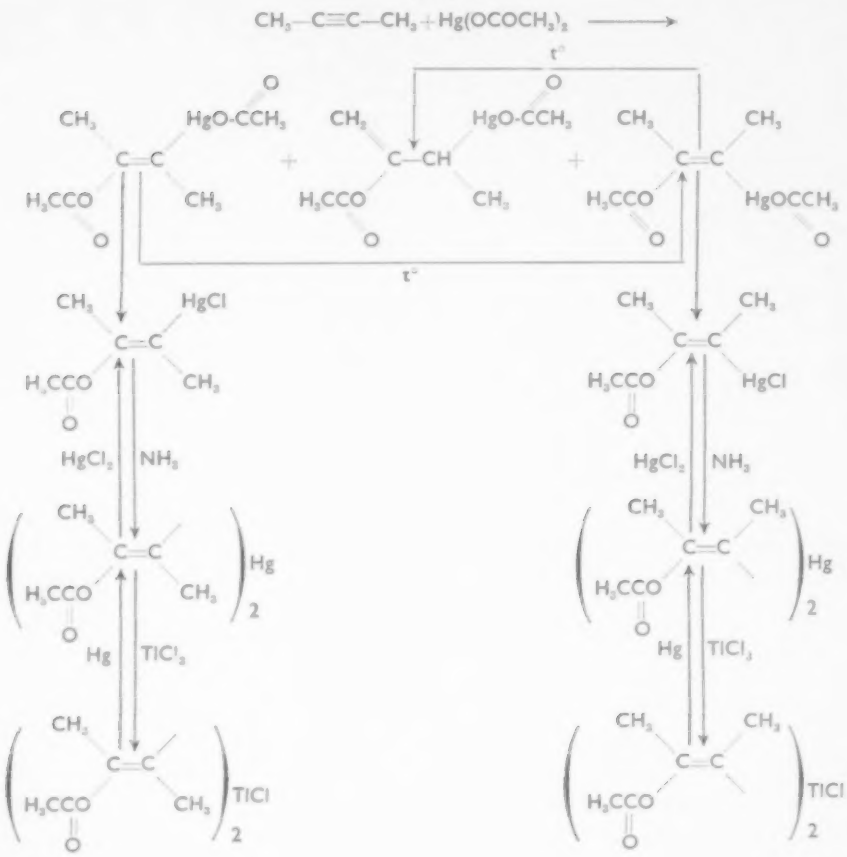
TABLE 2



effected in the reverse direction by reacting in the latter case with metallic mercury, and in the former with antimony. All reactions described are of a stereospecific type producing only one stereoisomer. In the same way *cis*-2-acetoxy-3-chloromercury-butene-2, m.p. 95°, appeared to undergo a symmetrical change to give the corresponding compound of the R_2Hg type, m.p. 101–102°, which by the action of thallium trichloride gives the stereoisomeride of the organo-thallium compound mentioned above. These reactions and the reverse ones take place similarly and are of a stereospecific type.

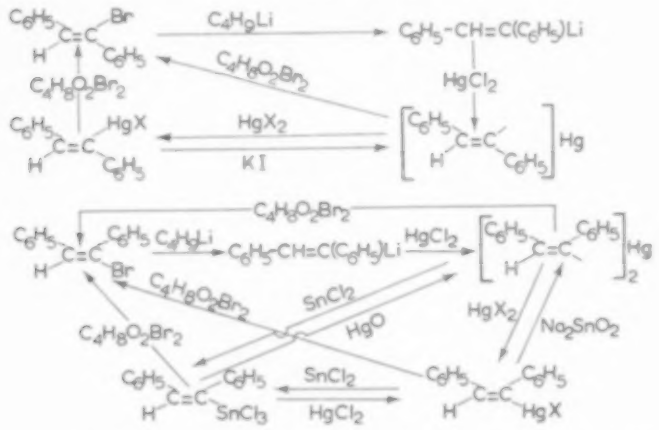
Both series of conversions are separated from each other and do not overlap. To this series of reactions the procedure of odd and even cycles cannot be applied. It is therefore to be assumed that either the configurations in all reactions are retained or that they are inverted in all instances. The latter is extremely unlikely, as the reaction $RHgX \rightarrow R_2Hg$ has in a number of instances been shown to proceed with the retention of the configuration. The possibility of inversion is to be discarded, as the mercury compounds shown in the left-hand column, obtained from *trans*-acetoxy-2-chloromercury-3-butene-2 exhibit a double-bond frequency

in the infra-red spectrum invariably higher than that of the corresponding stereoisomer. (*Trans*-acetoxy-2-chloromercury-3-butene-2, m.p. 140°/1667 cm^{-1}; *cis*-acetoxy-2-chloromercury-3-butene-2, m.p. 95°/1655 cm^{-1}; *trans*-di-(1-methyl-2-acetoxy-1-propene-1-il) mercury, m.p. 114°/1621 cm^{-1}; *cis*-isomer, m.p. 101–102°/1616 cm^{-1}).

This fact, as well as that of their higher melting-points, leads us to conclude that each column represents one stereochemical series, the left column undoubtedly indicating the trans configuration.

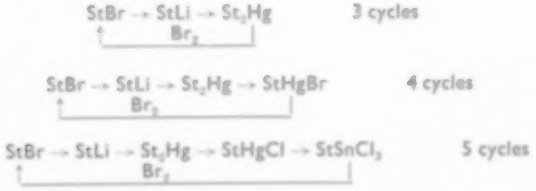
The following sequence of reactions, shown in Table 3:

TABLE 3



represents exchange reactions of stereoisomeric monobromostilbenes, carried out by us and N. A. Volkenau, using the procedure of odd and even cycles.[12] *Cis*- (m.p. 21°) and *trans*- (m.p. 32°) bromostilbenes were converted into lithium stilbenes under the action of butyllithium at −40°.

Lithiumstilbenes were immediately converted by the action of antimony into di-stilbenylmercury. Then followed the cyclic reactions represented in the scheme.* They were reconverted to their parent bromostilbene. With *cis*-bromostilbene the even and odd cycles are, for example, as follows:



Cis-lithiumstilbene is extremely sensitive to heat. Therefore, the reaction of bromostilbene with butyllithium has to be carried out at −40° (in ether-benzene

* The melting-points of compounds involved in this cycle of trans conversions are as follows: Bromostilbene 32°, chlorostilbene 53·5°, chloromercurystilbene 142°, bromomercurystilbene 157–158°, mercury-*bis*-stilbene 243–244°. Those of the *cis* series are: bromostilbene 31°, chloromercurystilbene 131°, bromomercurystilbene 118–120°, mercury-*bis*-stilbene 145–147°, stilbenyl-trichlorostannane 109–110°.

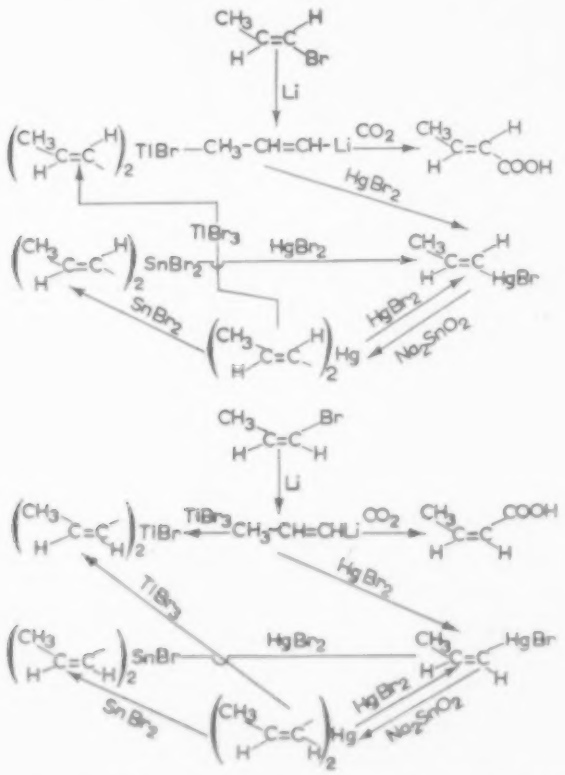
[12] A. N. Nesmeyanov, A. E. Borisov, and N. A. Volkenau *Izvest. Akad. Nauk SSSR*, 992 (1954); 162 (1956).

mixture) and the organo-lithium compound produced must at once be subjected to other reactions: otherwise, *cis*-lithiumstilbene results in compounds of the *trans* series. Experiments have shown that isomerisation does not take place during the reaction of substitution of bromine by lithium, but that it is the organo-lithium compound which is isomerised after formation. *Cis*-mercury-*bis*-stilbene can undergo isomerisation into a *trans* compound after prolonged heating (140°) or being irradiated with ultra-violet rays.

In other respects the compounds obtained from *cis*-stilbene are not similar to those derived from *trans*-bromostilbene. The succession of even and odd cycles proves in this case also the retention of the configuration in each step of the reaction.

Exchange reactions are represented in Table 4, starting from *cis*- and *trans*-1-bromo-propene-1, and were carried out and studied by us and N. V. Novikova.[13]

TABLE 4



In this case one can safely work at temperatures not exceeding room temperature. The formation of propenyllithium took place at 3–6°. Heating propenylmercury halogens dissolved in acetone at the boiling temperature is enough to bring about the interconversion of stereoisomers.

Similarly, prolonged standing (3–5 days) or heating for several hours up to 50° in benzene solution, results in far-reaching interconversion of stereoisomers of dipropenylmercury.

Exchange reactions involve the following cycles:

$Pr_2TlBr \rightleftarrows PrLi \rightleftarrows PrHgBr \rightleftarrows Pr_2Hg$ — 4 cycles

$PrHgBr \rightleftarrows Pr_2Hg \rightleftarrows Pr_2SnCl_2$ — 3 cycles

$Pr_2Hg \rightleftarrows Pr_2SnCl_2$ — 2 cycles

$Pr_2Hg \rightleftarrows PrHgBr$ — 2 cycles

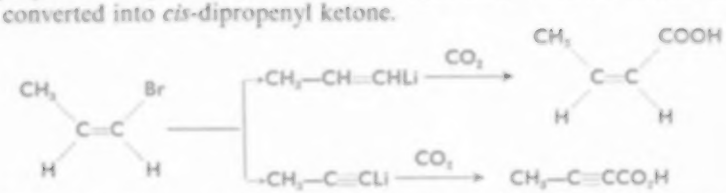
When the exchange reactions are being carried out at low temperature (or lower than room temperature), the fields of the conversions of *trans*-bromopropene and *cis*-bromopropene are isolated from each other.

From the double-bond frequencies in the infra-red spectrum of isomeric bromomercury-propenes it can be deduced that the bromomercury propene produced from trans-bromopropene has a trans configuration, as its frequencies (1625 cm^{-1}) are respectively higher than those of its isomer (1510 cm^{-1} and 1600 cm^{-1}).

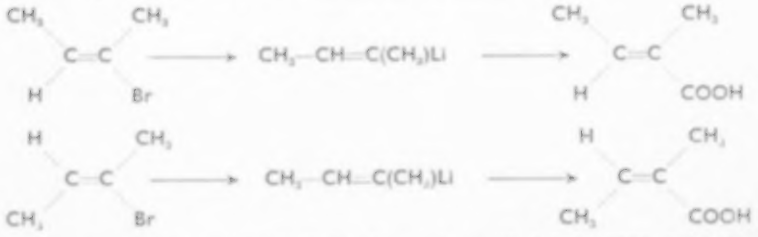
Thus, for the higher-melting (360°) dipropenylthallium bromide obtained from *trans*-bromopropene, the CH-bond frequencies have been found to be higher (1042 cm^{-1}, 960 cm^{-1}) than for its stereoisomer, produced from *cis*-bromopropene (1037 cm^{-1}, 926 cm^{-1}).

The assertion made by us in 1948, that electrophilic and homolytic substitutions at the olefinic carbon take place with retention of the configuration is now shown to be of an entirely general character.

In a paper published by Braude and Coles[14] it was stated that conversion of *cis*-bromopropene through an organo-lithium compound leads to *iso*crotonic acid which is then converted into *cis*-dipropenyl ketone.



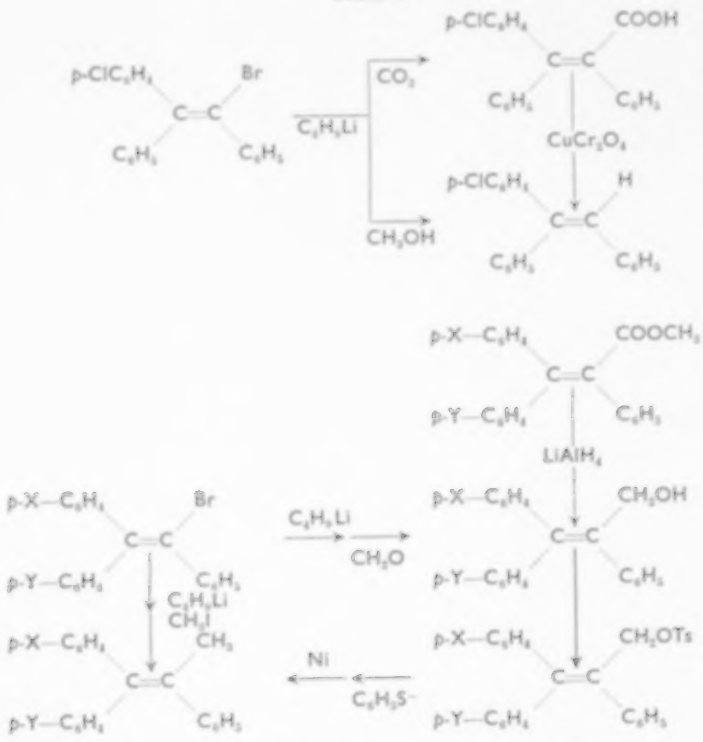
In 1954, Dreiding and Pratt[15] effected the carboxylation of organo-lithium compounds, obtained from both stereoisomers of 2-bromobutene-2, to yield acids with a configuration corresponding to that of parent bromides. In both cases the overall retention of the configuration does not prove the stereochemistry of each reaction taken separately, as two successive inversions are possible.



[13] A. N. Nesmeyanov, A. E. Borisov, and N. V. Novikova *Izvest. Akad. Nauk SSSR, Otdel. khim. Nauk* In press.
[14] E. A. Braude and J. A. Coles *J. Chem. Soc.* 2078 (1951).
[15] A. S. Dreiding and R. J. Pratt *J. Amer. Chem. Soc.* **76**, 1902 (1954).

The investigations of Curtin and Harris[16] and Curtin, Johnson, and Steiner[17] are represented in Table 5.

TABLE 5



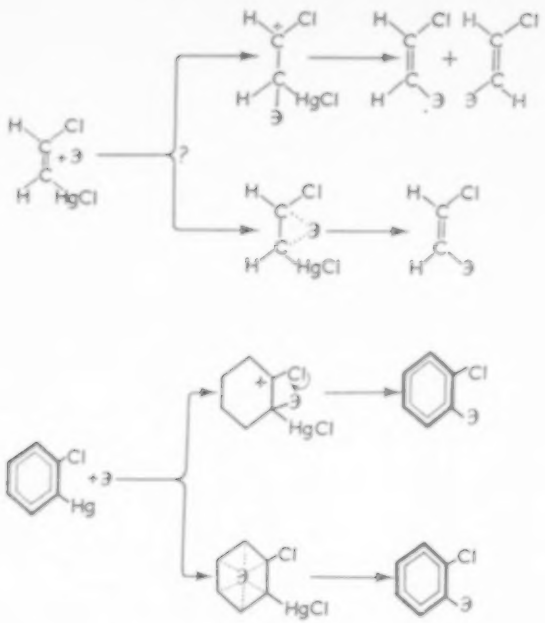
Cis-isomer X = Cl; Y = H; trans-isomer X = H; Y = Cl

These authors also demonstrate the overall retention of the configuration, but as can easily be seen, this overall retention can be explained in each case as due to two successive inversions.

Only in the light of the results of our investigation does it become certain that in the investigations of the above-mentioned authors each reaction proceeds without the inversion of the configuration. The retention of configuration in the reactions of electrophilic (and homolytic) substitution at the trigonal carbon is unexpected not so much in comparison with Walden's inversion as with the electrophilic substitution in the aromatic nucleus. The usual treatment of electrophilic substitution in the benzene nucleus in the case say of ortho chloro-mercury chlorobenzene may be compared with the similar exchange reaction of mercury in *cis*-chlorovinylmercury chloride.

A similar treatment of the substitution reaction of a metallic atom at the olefinic carbon inevitably leads to the inversion of the configuration of the parent olefinic

[16] D. J. Curtin and E. E. Harris *J. Amer. Chem. Soc.* **73**, 2716 (1951).
[17] D. J. Curtin, H. W. Johnson, and E. G. Steiner *J. Amer. Chem. Soc.* **77**, 4566 (1955).



substance. At the same time, it would be impossible to assume that the π bond—in the case of an olefine—should not have participated in the reaction.

The only plausible conclusion would be to assume the formation of a complex in the transition state retaining the configuration. If such be the case, analogous considerations make us think of a similar scheme for the substitution in the aromatic nucleus as the more probable and which is the Dewar scheme for electrophilic aromatic substitution.

VOL. 1 1957

Tetrahedron, 1957, Vol. 1, pp. 169–171. Pergamon Press Ltd., London

NOTES

Dehydrobrucinolone, *iso*brucinolone, and *iso*strychinolones-I and -II

(*Received* 28 *December* 1956)

LEUCHS and Brewster[1] oxidised crude brucinolone-B acetate with permanganate in acetone and obtained a small amount of a compound analysing as $C_{23}H_{22}O_6N_2$ or $C_{23}H_{24}O_6N_2$. Later, this substance was obtained by heating brucinolone-C in acetic anhydride containing sodium acetate. It was suggested[2] that it was the acetate of either a dehydrobrucinolone or of an unknown brucinolone. The acetyl group could be removed with methanolic ammonia to give a compound $C_{21}H_{20}O_5N_2$ or $C_{20}H_{22}O_4N_2$.

In attempting to repeat this work we obtained only brucinolone-C acetate on heating brucinolone-C in acetic anhydride as directed. However, when brucinolone-C acetate was heated with one equivalent of benzoyl peroxide in acetic anhydride, a good yield of an acetate $C_{23}H_{22}O_6N_2$ was obtained, which from its analysis and mode of formation must be dehydrobrucinolone acetate. Similarly, brucinolone-B or -C, heated with benzoyl peroxide in acetic acid, gave dehydrobrucinolone, agreeing closely in properties with Leuchs' ammonolysis product.

The ultra-violet absorption curves of dehydrobrucinolone and its acetate were identical (λ_{max} 237, 311, 350 mμ; log ε_{max} 4·3, 3·7, 3·9 respectively). These resemble the absorption curve for dehydrostrychninolone[3] (λ_{max} 340 mμ; log ε_{max} 3·9); the additional peak at 311 mμ is to be ascribed to the effect of the methoxyl groups.[4] Dehydrobrucinolone must consequently possess the *N*-phenyl-α-pyridone structure like dehydrostrychninolone.

*iso*Brucinolone[1] has the same ultra-violet absorption as brucine and so must be a $\beta\gamma$-unsaturated amide,[5] confirming some rather tentative evidence from oxidation experiments.[6]

*iso*Brucinolone must, consequently, be epimeric with brucinolone-B at $C_{(21)}$. The shift in molecular rotation (Δ) attendant on the inversion at this centre is approximately the same as that in going from strychninolones-B and -C to the *iso*strychninolones-I and -II[7] as shown below. Hence, the two latter compounds probably have the $\beta\gamma$- and $\alpha\beta$-unsaturated amide structures respectively.

MOLECULAR ROTATIONS

				Δ value
Brucinolone-B	−91·7°	*iso*Brucinolone	+129·9°	+221·6°
Strychninolone-B[5]	−77·3°	*iso*Strychninolone-I[7]	+148·1°	+225·4°
Strychninolone-C[5]	−565·5°	*iso*Strychninolone-II[7]	−504·7°	+157·8°

EXPERIMENTAL

Brucinolone-C. The following method was found to be considerably more convenient than that published.[2] Crude brucinolone-B (4·0 g) in pyridine (40 c.c.) and 2·5% sodium hydroxide solution (160 c.c.) was heated on the steam-bath for 90 min. The acidified solution was extracted with chloroform (5 × 10 c.c.), and the dried chloroform-extract passed through a short column of alumina. The residue crystallised from methanol in needles (1·1 g), m.p. 180–184°, raised to 185–186° by a second crystallisation from methanol, $[\alpha]_D^{15}$, −147° (*c.* 0·184 in acetic acid).

Dehydrobrucinolone. Brucinolone-C (0·40 g) and benzoyl peroxide (0·25 g) in glacial acetic acid (5 c.c.) were heated on the steam-bath for 30 min. The solution, on dilution with water, gave brown needles of dehydrobrucinolone (0·1 g), m.p. 299–301°. Recrystallisation from ethanol (charcoal)

[1] Leuchs and Brewster *Ber.* **45,** 201 (1912).
[2] Leuchs and Pierce *ibid.* p. 2653; Leuchs, Hellriegel, and Heering *Ber.* **54,** 2177 (1921).
[3] Prelog, Kocor, and Taylor *Helv. Chem. Acta* **32,** 1052 (1949).
[4] Prelog and Szpilfogel *ibid.* **28,** 1669 (1946).
[5] Prelog, Szpilfogel, and Battegay *ibid.* **30,** 366 (1947).
[6] Leuchs, Gladkorn, and Hellriegel *Ber.* **56,** 2472 (1923).
[7] Leuchs and Ritter *Ber.* **52,** 1583 (1919).

furnished pale fawn needles, sintering at 295°, m.p. 307–310° (dec.), $[\alpha]_D^{20}$? −388° (*c*. 0·34 in acetic acid) (Found in air-dried material: C, 58·7, 58·9; H, 5·9, 6·0. Calc. for $C_{23}H_{26}O_5N_2$, 2·5 H_2O: C, 59·0; H, 6·4%. Found in material dried at 130°/15 mm: C, 65·9; H, 5·2; N, 7·4. Calc. for $C_{23}H_{26}O_5N_2$: C, 66·3; H, 5·3; N, 7·4%). Dehydrobrucinolone gave a yellow colour, rather than the usual orange-red of brucine derivatives, with nitric acid.

Dehydrobrucinolone acetate. Brucinolone-C acetate (0·6 g) and benzoyl peroxide (0·35 g) in acetic anhydride (5 c.c.) were warmed on the steam-bath for 1 hour. The yellow solid (0·4 g) which separated was crystallised from ethanol as fine yellow needles, sintering at 290°, m.p. 304°, $[\alpha]_D^{20}$, −429° (*c*. 0·892 in acetic acid) (Found: C, 65·5; H, 4·9; N, 6·4. Calc. for $C_{25}H_{22}O_6N_2$: C, 65·4; H, 5·2; N, 6·6%).

Grateful acknowledgement is made to the Royal Commission for the Exhibition of 1851 for a Science Scholarship (to J. T. E.).

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VOL. 1 1957

Note on the transmission of free radical character through a conjugated system

(*Received* 30 *January* 1957)

In an early paper entitled Polarisation of Nitrosobenzene[1] the author drew attention to the possible overlapping "enoid" and "onoid" conjugated systems in nitrosobenzene and suggested that they might be present together in this and simliar cases

enoid displacement or polarisation

onoid displacement or polarisation

Although the interpretation which follows was not excluded by the language used, the intention was to postulate *activations* in two different senses, both of which were feasible. The emphasis was on the *electron displacements* responding to the approach of a reagent rather than on the hybridisation within the normal molecules resulting from the opposing tendencies. Subsequently, in lectures and university teaching the idea of polarisation in the course of a reaction was always prominent. It is by no means the present intention to abandon this conception, which certainly must always apply to the completion stages of a reaction process. But it is now desired to point out that the electronic conditions may be such that a reaction can be *initiated* in either sense in the normal molecules, identifiable sites in which may possess free radical character and hence may be at the same time electron-donor and electron-acceptor in quality.

Furthermore, free radical character may be transmitted along a conjugated chain exactly as we originally postulated the transfer of unshared electrons or electron defect.[2]

The fundamental character of a free radical site is that the atom concerned has both (1) unshared electron or electrons and (2) an incomplete electron configuration. In regard to (1), every atom is potentially an electron-donor if it bears an unshared electron (or electrons), even if the electrical field at the point considered is positive. It is generally true that an adverse electrical field will diminish in varying degree the ease with which electron coupling or electron-nucleus coupling occurs but it does not totally prohibit such events. It is even possible for an atom site to have an actual electrical charge and to accept or donate electrons in the opposite sense. A^+ can donate electrons if it bears any that are unshared, and B^- can accept electrons if the B configuration is incomplete.

The well-known fact that free radical reagents attack the *p* position of monosubstituted benzenes whatever the reaction of the substituent, is clearly due to the two circumstances (1) that conjugated aromatic systems are always activated in the *p* (or *o*) position, which either acquires unshared electron

value or becomes configurationally defective in electrons and (b) that free radicals can either accept or donate electrons.

It should be noted that when two identical atoms or free radicals unite, $R^{\times}$ and $R^{\times}$ giving $R^{\cdot}_{\cdot}R$, the question of electron donor or acceptor becomes meaningless. However, when $A^{\times}$ joins with $B^{\times}$ to $A^{\cdot}_{\cdot}B$, there may be a recognisable distinction.

Free radicals can therefore be classified in accordance with these proclivities, but this interesting side-issue need not be pursued for the present purpose. It may, however, be noted that a classification could be predicted on theoretical grounds, or based on experimental observation of the relative proneness of a series of free radical reagents to attack systems with unshared electron sites, or those defective in electron configuration. Returning to the case of nitrosobenzene, it will now be clear that the *p*-carbon atom has free radical character in accordance with the above analysis. The "enoid" and "onoid" systems are now assumed to operate together and reach a hybrid.

This type of "push-pull" double displacement originates in the peculiar nitroso group, but it will be apparent that conjugated relay is theoretically feasible beyond the *p*-position, as shown in the symbol:

Here C-*x* corresponds to the *p*-position in nitrosobenzene and its character is relayed to C-*y*.

There are many applications of these views which will later be considered in more detail. An interesting example is pyridine-*N*-oxide

"enoid" *"onoid"*

The simultaneous occurrence of the two types of displacement shown gives free-radical character to C-4.

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[1] R. Robinson *J. Soc. Chem. Ind. XLIV*, 456 (1925).
[2] W. O. Kermack and R. Robinson *J. Chem. Soc.* **121**, 427 (1922).

Tetrahedron, 1957, Vol. 1, pp. 172–175. Pergamon Press Ltd., London

PRELIMINARY COMMUNICATIONS

The chemistry of akuammicine

(*Received* 11 *February* 1957)

VOL. 1 1957

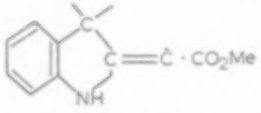
THE alkaloids of the seeds of *Picralima Klaineana* Pierre were first isolated and studied by Henry and Sharp[1] and Henry,[2] and later by Millson, Robinson, and Thomas,[3] who used seeds of *Picralima nitida* Stapf. (= Klaineana; the genus has only one species) obtained through the good offices of the Colonial Products Research Council.

The present authors have worked up a second batch of seeds from the same source, and are grateful to Dr. R. A. Galley for the provision of this material. Akuammicine is found among the bases soluble in light petroleum, and *n*-hexane was used in the present work. It is of special interest because of its high specific rotatory power, −737·7°, and it exhibits a number of very characteristic colour reactions. Raymond Hamet[4] has shown that the ultra-violet absorption of akuammicine is of indoline type and very similar to that of echitamidine, which also has an abnormally high rotatory power.

Henry's formula for akuammicine was $C_{19}H_{20}O_2N_2$, but Robinson and Thomas[5] proposed to change this to $C_{20}H_{22}O_2N_2$. We have confirmed the C_{20} formula by repeated analyses, especially of the methiodide and *picrate*.

Akuammicine is a strong base, pK_a, 7·45;[5] it contains 1 Me(C) and 1 Me(O) and affords on catalytic hydrogenation a dihydro-derivative which exhibits the same ultra-violet absorption as the parent base. Infra-red absorption indicates an *o*-disubstituted benzene nucleus, an —NH· group, and includes a strong band at 6·03 Å which was at first thought to be due to :N·CO.

This hypothesis was later found to be untenable, though it was the chemical evidence which led us to the realisation that the alkaloid probably contains the group.

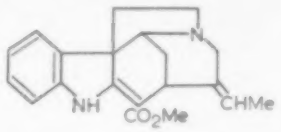


Confirmation was then available in the fact that the ester, Ph·NH·CMe=CH·CO_2Et, absorbs at 6·03 Å.

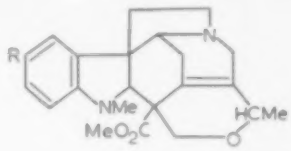
Robinson and Thomas found that akuammicine was resistant to lithium aluminium hydride, but, working under more vigorous conditions, we found that reduction could be effected by this reagent and the product was a crystalline base, $C_{19}H_{22}N_2$, showing typical indoline absorption and reactions. With Ehrlich's reagent it gave an intense orange-yellow coloration, which is a characteristic reaction for *sec*-aromatic amines. The composition change could be explained as $-CO_2Me \rightarrow CH_3$, and the new base did not contain methoxyl. The Me(C) content was augmented, but the values found were low both for akuammicine and the reduction product. These deductions were confirmed by the results of hydrolysis. With methanolic potassium hydroxide the methoxyl is removed, but the product is an intractable amino-acid. Careful acid hydrolysis afforded a base, $C_{18}H_{20}N_2$, which was oxidised readily on exposure to the air. The loss of CO_2 as well as Me is readily understood, on the basis that ϕ·NH·Ċ = Ċ·CO_2Me is a vinylogue of ϕ·NH·CO_2Me.

[1] T. A. Henry and T. M. Sharp *J. Chem. Soc.* 1950 (1927).
[2] T. A. Henry *J. Chem. Soc.* 2767 (1932).
[3] M. F. Millson, R. Robinson, and A. F. Thomas *Experientia* IX/3, 89, (1953).
[4] Raymond Hamet *Compt. Rend.* **211,** 125 (1940); **221,** 69, 699, (1945); **230,** 1183 (1950); **233,** 560 (1951); *Arch. Exp. Path. Pharm.* **199,** 399 (1942); *Compt. Rend. Soc. Biol.* **137,** 404 (1943); **138,** 199 (1944); **148,** 458 (1954); *Rev. Int. Bot. App. Agric. trop.* **31,** 465 (1951); *Bull. Soc. Pharm. Bordeaux* **90,** 178 (1952);
[5] R. Robinson and A. F. Thomas *J. Chem. Soc.* 2049 (1955).

On the biogenetic grounds generally accepted as applicable to the indole alkaloids, we developed the structure of akuammicine to (I).



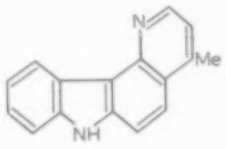
I



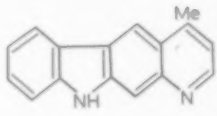
II

It is thus assigned to the β-series of indole alkaloids and the position of the $\cdot CO_2Me$ is the same as that proposed for akuammine (II, R = OH) and *pseudo*-akuammigine (II, R = H) quite independently and on different grounds.[6] It was already known that akuammine affords β-ethylpyridine on distillation over zinc dust,[5] and we have found that *pseudo*-akuammigine behaves in the same way; also that carbazole is produced in the former reaction. The zinc-dust distillation of akuammicine also yields β-ethylpyridine, along with simple but unidentified indole derivatives.

The degradation by heating with selenium gave skatole and β-ethylindole (isolated as a mixture of their picrates) and a new base, $C_{16}H_{12}N_2$, which we propose to name *akuammicyrine*. The most natural structure that could be assigned to this substance is III



III



IV

Syntheses of the indolo-lepidines (III) and (IV) have been effected. 7-Hydrazino-4-methylquinoline was submitted to Fischer indole synthesis with *cyclo*hexanone and the product dehydrogenated to III. The linear isomeride (IV) was made from 7-hydrazino-4-methyl-2-quinolone by the Fischer reaction with *cyclo*hexanone followed by chlorination of the product with phosphoryl chloride hydrogenation in presence of Raney nickel and potassium hydroxide in ethanol, and dehydrogenation by means of palladised charcoal in boiling cymene.

The base (III) is closely similar to akuammicyrine in ultra-violet absorption. The behaviour of mixtures of the picrates on heating neither proves nor disproves identity, and the matter will be further investigated. Meanwhile the ultra-violet absorption curves are so similar that there can be little doubt but that akuammicyrine contains the basic skeleton of III. Conceivably the methyl group is differently sited or perhaps partly eliminated.

The composition, $C_{20}H_{26}O_2N_2$, was assigned to echitamidine,[7] which is akuammicine plus 4H and O. It is not easy to modify the structure (I) to fit this in view of the hypothesis that the high rotatory power is associated with unsaturation.

If the base were $C_{20}H_{24}O_3N_2$ (C analysis, 1% low), it could be a hydroxy-dihydro-akuammicine.

Half of its (N) or (O) methyl is given as methoxyl and half as methylimino. Goodson thought the labile Me(N) choice the better, but we suggest that a $-CO_2Me$ is present and the cause of the curious analytical results may be that a part of the methyl content wanders from O to N during the Zeisel operation. Analogies for this supposition are readily accessible.

Tabersonine[8] is probably a third member of this small group of alkaloids.

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K. AGHORAMURTHY
R. ROBINSON

[6] R. Robinson and A. F. Thomas *J. Chem. Soc.* 3552 (1954); cf. F. E. Bader *Helv. Chim. Acta* **36**, 215 (1953).
[7] J. H. Goodson *J. Chem. Soc.* 2626 (1932).
[8] M. M. Janot, R. Goutarel and J. Le Men *Bull. Soc. Chim.* (*France*) 707 (1954).

Secondary hydrogen isotope effects as a criterion of mechanism

(*Received* 4 *March* 1957)

SECONDARY hydrogen isotope effects, first discovered in S_N1 solvolyses,[1,2] have now been observed in additional reactions, and appear to be attaining the status of a mechanistic criterion.[3–5] These effects are commonly interpreted as arising from the difference in "zero point" vibrational energy between the initial state and the activated complex, leading to less effective hyperconjugative stabilisation of the latter in the case of β- (and *para* methyl) deuterated compounds. The possibility that C-D and C-H bonds may differ in their *ground-state* inductive effects, and that the electron distribution in the isotopic molecules may thus not be identical, has been either ignored[1–5] or specifically discounted.[6]

It has been shown that α-deuteration leads to decreased acidity in phenylacetic acid and to increased basicity in benzylamine.[7] In these instances, ground-state differences must be involved, and these presumably derive from differential inductive electron release, which is *stronger* from C-D than from C-H bonds. The existence of small differences in the polar properties of several isotopic molecules are well known,[8–10] and these have been ascribed to a slight disparity in their mean molecular configurations, resulting from anharmonicity, which is appreciable even in the vibrational ground states.[9,11] A simple treatment of these polarity differences is the subject of a forthcoming publication.

The solvolytic reactions referred to above are subject to predominant electromeric, in this case hyperconjugative influences,[12] though even here the solvent dependence of the isotope effect,[13] suggests that more than one factor is operative. In other reactions, inductive effects are often of comparable, or even primary importance, and the neglect of an inductive contribution to the isotope effect is by no means justified.

Several apparently anomalous recent observations can be reconciled on the basis of these considerations:

(a) The retardation of base-catalysed enolisation in β-deuterated ketones[5] becomes reasonable in terms of the established mechanism,[14] and certainly does not refute it as claimed.

(b) The slight acceleration of the decomposition of methyl-deuterated *p*-toluenediazonium ion,[4] a reaction subject to both inductive and hyperconjugative influences, may well result from a balance between two opposing isotope effects.

(c) Similarly, since the inductive and hyperconjugative effects of alkyl groups are of roughly comparable importance in electrophilic aromatic substitution,[15,16] the failure to observe an appreciable secondary isotope effect in some aromatic substitutions,[17] may also be due to a fortuitous cancelling

[1] E. S. Lewis *et al.* *J. Amer. Chem. Soc.* **74,** 6306 (1952); **76,** 791, 796, 1603 4495 (1954).
[2] V. J. Shiner, Jr. *Ibid.* **75,** 2925 (1953); **76,** 1603 (1954); **78,** 2653 (1956).
[3] C. E. Boozer, B. W. Ponder, J. C. Trisler, and C. E. Wightman *Ibid.* **78,** 1506 (1956).
[4] E. S. Lewis, J. L. Kinsey, and R. R. Johnson *Ibid.* **78,** 4294 (1956).
[5] W. D. Emmons and M. F. Hawthorne *Ibid.* **78,** 5593 (1956).
[6] A. Streitwieser, Jr., R. H. Jagow, and S. Suzuki *Ibid.* **77,** 6713 (1955).
[7] E. A. Halevi and M. Nussim *Bull. Res. Council Israel* **5-A,** 263 (1956); *Ibid.* Abstracts of the 20th Meeting of the Israel Chemical Society, Haifa, December 3, 1956.
[8] J. M. A. de Bruyne and C. P. Smyth *J. Amer. Chem. Soc.* **57,** 1203 (1935).
[9] R. P. Bell and I. E. Coop *Trans. Faraday Soc.* **34,** 1209 (1938).
[10] J. W. Simmons and J. H. Goldstein *J. Chem. Phys.* **20,** 122 (1952).
[11] S. L. Miller, L. C. Aamodt, G. Dousmanis, C. H. Townes, and J. Kraitchman *Ibid.* **20,** 1112 (1952).
[12] C. K. Ingold *Structure and Mechanism in Organic Chemistry* p. 326. Cornell University Press (1953).
[13] V. J. Shiner, Jr. and C. J. Verbanic *J. Amer. Chem. Soc.* **79,** 373 (1957).
[14] Reference 12, Chapter X.
[15] *Ibid.* p. 258.
[16] P. B. D. de la Mare and J. T. Harvey *J. Chem. Soc.* **1957,** 131.
[17] C. G. Swain, T. E. C. Knee, and A. J. Kresge *J. Amer. Chem. Soc.* **79,** 505 (1957).

of increased effective electropositivity on the one hand, and decreased hyperconjugative stabilisation of the activated complex on the other.

Experiments are now under way designed to assess the relative importance in different circumstances of static vs. dynamic and of inductive vs. hyperconjugative influences in secondary hydrogen isotope effects. Only when such an evaluation has been made, will they afford unambiguous mechanistic conclusions.

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EDITORIAL NOTE

In view of the large number of papers submitted for this first issue of *Tetrahedron*, it has been decided to publish the present double issue of 176 pages in order to avoid publishing delays.

However, the single issues of *Tetrahedron* will normally consist of approximately 100 pages and the Volume as a whole will contain approximately 400 pages.

The next issue, which will be Issue Number 3 of the Volume, will be published, as planned, in July.

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Tetrahedron, 1957, Vol. 1, pp. 177–185. Pergamon Press Ltd., London

THE STRUCTURE OF DENDROLASIN

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(*Received* 7 *March* 1957)

Abstract—The chemical and i.r. spectrographic study of *dendrolasin*, the odorous substance $C_{15}H_{22}O$ isolated from the ant *Lasius* (*Dendrolasius*) *fuliginosus* Latr., indicates that it possesses a β-substituted furan structure containing a sesquiterpenoid skeleton formed by head to tail union of three isoprene units. Dendrolasin is, most probably, β-(4:8-*dimethylnona*-3:7-*dienyl*) *furan* (I). Catalytic hydrogenation affords, depending on the conditions, a tetrahydroderivative which is still a furan, and an octahydroderivative which is a tetrahydrofuran. Permanganate oxidation of dendrolasin yields acetone and succinic acid; on ozonolysis, besides these two products, levulinic aldehyde is also formed.

THE odorous substance which we isolated from the ant *Lasius* (*Dendrolasius*) *fuliginosus* Latr. was designated as *dendrolasin*. As previously described in a short paper,[1] this product is contained in the mandibular glands secretion of the insect. It can be isolated in a fairly pure state by fractionation under reduced pressure of the oil obtained by steam distillation of a light petroleum extract of the ant, from which the solvent had been previously removed. 8–10 kg of insect yield 60–70 ml of oil containing about 75 per cent of dendrolasin.

Dendrolasin, $C_{15}H_{22}O$, is a colourless oil with a lemon-grass odour, b.p. 148°–150°/16 mm, n_D^{20} 1·486, d_4^{20} 0·9108. It is optically inactive, exhibits a neutral character and is not dissolved by dilute alkalis or acids. It polymerises on long keeping into a viscous oil. Strong mineral acids, particularly nitric and sulphuric acids, transform dendrolasin into resinous products. It is readily attacked by bromine in the presence of water giving a nearly colourless resin.

Dendrolasin is indifferent towards hydrazine hydrate, *p*-nitrophenylhydrazine, semicarbazide hydrochloride and phenyl *iso*cyanate. It does not condense with maleic anhydride in hot toluene solution. With mercuric chloride or acetate it affords white solid compounds which could not be isolated in the pure state.

Dendrolasin gives the following characteristic reactions:

(a) Its solution in glacial acetic acid becomes orange-red colour when treated with a drop of conc. sulphuric acid.

(b) Acetic anhydride dissolves dendrolasin giving a dirty violet solution which turns rapidly black.

(c) A pine shaving, moistened with conc. HCl, acquires a dirty blue-green colour in contact with dendrolasin.

(d) With vanillin in HCl-ethanol solution at room temperature, it gives a fine fuchsia-red colour, which becomes very intense on heating, and turns finally to olive brown. A similar reaction is shown on heating with Ehrlich's reagent.

The inactivity of dendrolasin towards reagents for the carbonyl group and to phenyl *iso*cyanate, indicates that it is not an aldehyde, ketone or alcohol. On the other hand, the above described colour reactions, its stability towards alkalis and sensitivity to acids, and its capacity to give complexes with mercuric salts, pointed to a

[1] A. Quilico, F. Piozzi, and M. Pavan *Ric. Sci.* **26**, 177 (1956); M. Pavan *Ibid.* **26**, 144 (1956).

furan derivative. Taking into account the empirical formula, two double bonds should be present in side chains.

The *i.r. spectrum* (Fig. 1, No. 1) of dendrolasin strongly supports this hypothesis. No band which could be attributed to a CO or OH group is present, whereas many bands, most of them very intense, can be assigned to a furanoid system. Such are the

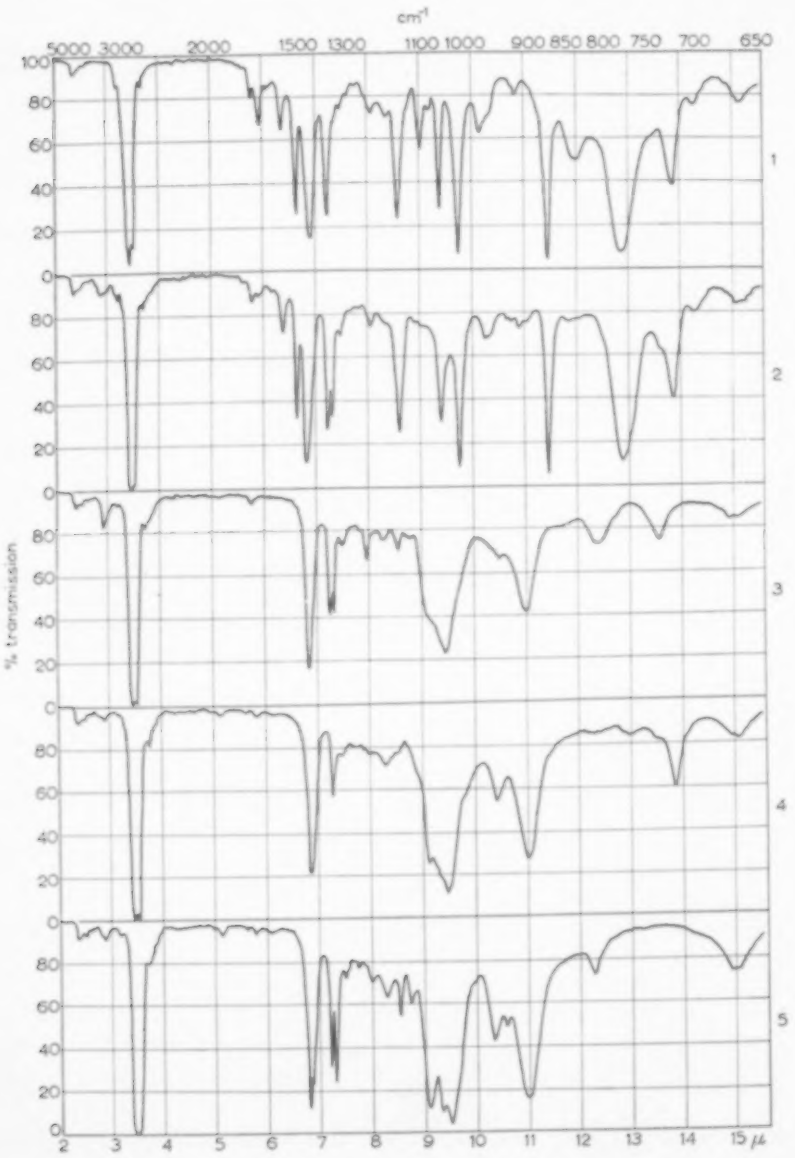

FIG. 1.—i.r. Spectra.

1. Dendrolasin; liquid 0·025 mm
2. Tetrahydroden drolasin; liquid 0·026 mm
3. Perhydrodendrolasin; liquid 0·022 mm
4. β-*n* Heptyltetrahydrofuran; liquid 0·025 mm
5. β-i-Butyltetrahydrofuran; liquid 0·024 mm

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bands at 1565; 1504; 1164; 1065; 1028; 874 and 779 cm^{-1}.* The two bands at 1679 and 834 cm^{-1} are probably due to aliphatic double bonds of the type —CH=C<.

Scanty information on the structure of dendrolasin is obtained from its *u.v. spectrum* in ethanol solution (Fig. 2a). It shows a practically continuous absorption between 220 and 350 mμ, with some inflections and no peak. It is generally similar to the spectra of some terpenic alcohols such as geraniol and farnesol (Fig. 2c),[2]

Catalytic hydrogenation of dendrolasin at the ordinary pressure and temperature, both in acetic acid solution over PtO_2 and in ethanol in the presence of Raney nickel or Pd—C, yields an octahydroderivative; $C_{15}H_{30}O$.

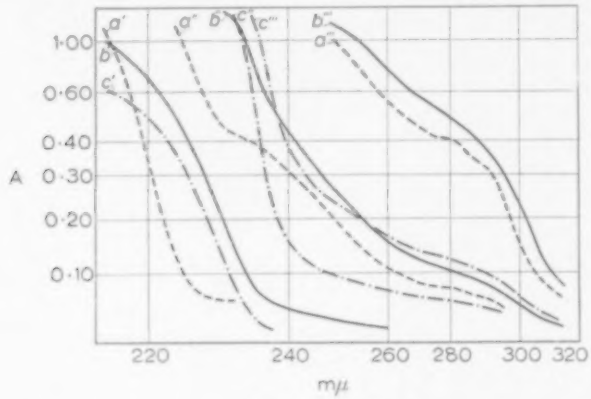


FIG. 2.—u.v. Spectra.

Farnesol	a' 56·76 mg/l.	a'' 567·6 mg/l.	a''' 2838 mg/l.
Dendrolasin	b' 32·48 mg/l.	b'' 324·8 mg/l.	b''' 1624 mg/l.
Tetrahydrodendrolasin	c' 33·32 mg/l.	c'' 646·4 mg/l.	c''' 1616 mg/l.

Perhydrodendrolasin thus obtained is an odourless liquid b.p. 155°/15 mm, n_D^{20} 1·4478, which does not give the pine shaving reaction and the red colour with vanillin. Its *i.r. spectrum* (Fig. 1, No. 3)† is characterised by the total disappearance of the bands belonging to the furan system and the occurrence, at about 1060 and 910 cm^{-1}, of two broad bands which can be assigned to the saturated tetrahydrofuran ring. The presence at 1383 and 1364 cm^{-1} of the *iso*propyl group bands, associated with the absence of those at 1679 and 834 cm^{-1} belonging to the —CH=C< group, indicates that an *iso*propylidene group (C)=C$(CH_3)_2$ is contained in dendrolasin.

If dendrolasin is actually a furan derivative containing two double bonds in side chains, we might expect that from its hydrogenation is suitable conditions, a saturated furan $C_{15}H_{26}O$, could be obtained.

The determination of the appropriate experimental conditions to achieve this result has been very laborious, because of the difficulty of arresting the process at the required

* Most of these bands appear to be shifted from the position they normally occupy in α-substituted furans which, in addition to the fundamental member of the series, are practically the only furan derivatives of which i.r. spectra data are available. This fact, in union with the aspect of the u.v. spectrum of dendrolasin and some peculiarities in its chemical behaviour, led us to the conviction that we were dealing with a β-derivative.

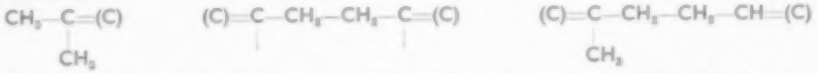
† Sample prepared in ethanol solution over Raney nickel. The i.r. spectra of specimens obtained with PtO_2 in acetic acid show weak bands assignable to OH and CH_3COO groups, indicating that hydrogenolysis of the tetrahydrofuran ring, followed by esterification, has partially occurred.

[2] Y. R. Naves and P. Ardizio *Helv. Chim. Acta* **31**, 1240 (1948); F. Bader *Ibid.* **34**, 1632 (1951).

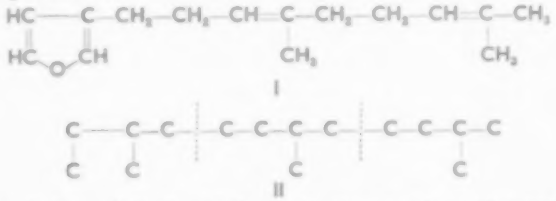
stage. Eventually we succeeded by the use of a mixture of Pd—C and Pd—$BaSO_4$ as the catalyst.

Tetrahydro-dendrolasin is a colourless liquid, b.p. 160°/15 mm, n_D^{20} 1·4855. Its *i.r. spectrum* (Fig. 1, No. 2) is closely similar to that of dendrolasin. The bands at 1565; 1504; 1163; 1065; 1027; 874 and 778 cm^{-1} are due to the furan ring; the bands at 1383 and 1366 cm^{-1}, to the *iso*propyl group. The colour reactions with vanillin and the pine shaving test are practically the same as with dendrolasin.

Important information about the number and the structure of the side chains has been supplied by the permanganate oxidation and ozonolysis of dendrolasin. Aqueous $KMnO_4$ attacks dendrolasin, slowly in the cold and more rapidly at 100°, giving *acetone* and *succinic acid*. On ozonolysis in ethyl acetate solution several products are formed; among them *acetone* (in the form of its dimeric peroxide), *levulinic aldehyde* and *succinic acid* have been isolated and identified. The formation of these substances indicates that the following structural units must be present in dendrolasin:



Taking these typical degradation products into account as well as the i.r. spectra data and the colour reactions and the very probable presence of a furan nucleus, also a general similarity to the terpenoid substances, it appears likely that dendrolasin possesses a terpenoid structure. This could be formed by the union of three isoprene units,[3]* one of them oxygenated and involved in the formation of the furan ring. Among the different structures which could be assigned to dendrolasin on this basis formula (I), derived from the head to tail union of three isoprene units as shown in (II), is the most probable:

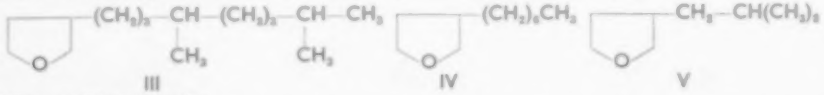


I

II

A *β-(4:8-dimethylnona-3:7-dienyl) furan* structure such as (I) would account for the lack of optical activity of dendrolasin, for its colour reactions,[4]† for the formation of acetone, levulinic aldehyde and succinic acid on ozonolysis, and would be consistent with the i.r. and u.v. spectra of this substance.

Attempts to synthesise dendrolasin and its hydroderivatives are in progress. Meanwhile indirect evidence for the structure (I) is provided by the results of i.r. spectra studies of some synthetic models of perhydrodendrolasin (III):‡



III IV V

* Or senecioic acid units.

† According to Reichstein *et al.*, α or β-monosubstituted furans give a bluish green colour in the pine shaving test, whereas with disubstituted furans the colour is violet-red.

‡ The preparation of these substances and of other β-substituted tetrahydrofurans will be described in a subsequent paper.

[3] R. Robinson *The Structural Relations of Natural Products* p. 15. Oxford (1955).

[4] Reichstein *et al.*, *Helv. Chim. Acta* **15**, 1110 (1932); *Ibid.* **16**, 28 and 37 (1933).

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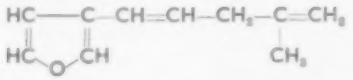
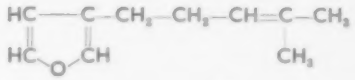
The i.r. spectrum of *β-n*-heptyltetrahydrofuran (IV) (Fig. 1, No. 4), shows at about 1060 and 910 cm^{-1} the characteristic bands due to the hydrogenated furan ring which are present in the i.r. spectrum of perhydrodendrolasin. Naturally, in spectrum No. 4 the bands of the *iso*propyl group are absent, whereas the band at 723 cm^{-1} belongs to the long saturated chain $(—CH_2—)_6$. In *β-iso**butyltetrahydrofuran* (V) i.r. spectrum (Fig. 1, No. 5) the broad band at about 1060 cm^{-1} appears resolved into a group of bands; absorption due to the *iso*butyl group is evident in the 1365–1390 cm^{-1} region.

Further support to formula (I) is given by the occurrence in nature of two *β*-monosubstituted furan derivatives of unequivocal isopentanoid structure, which closely resembles dendrolasin both in their physical and chemical properties. Both *α-clausenane* (VI)[5] and *perillene* (VII)[6] are formed by head-to-tail linking of two isoprene units:*

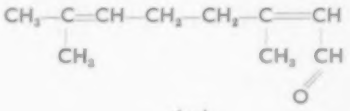


VI

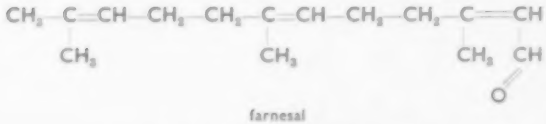


VII

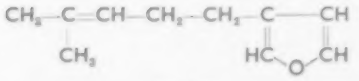
Particularly striking is the similarity between dendrolasin and perillene; both show the same colour reactions and behave in the same way towards catalytic hydrogenation and ozonolysis. It is interesting to notice that the evident structural relations existing between citral (or geraniol) and perillene in the C_{10} series, would find a corresponding relationship in the C_{15} series between farnesal (or farnesol) and dendrolasin, as shown by the scheme:



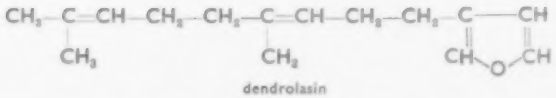
citral



farnesal



perillene



dendrolasin

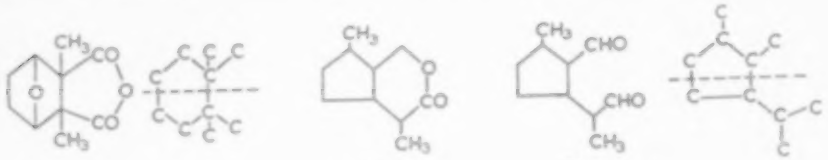
* Other furans occurring in nature and containing the isoprene skeleton are: *β*-furoic acid, from the roots of *Evonimus atropurpureus* and *Phaseolus multiflorus; β-iso*amyl furyl ketone, from the essential oil of *Perilla frutescens*, and *α-iso*valeroyl-*β*-methyl furan from the roots of *Elshozia cristata*.

[5] B. S. Rao and K. S. Subramanian *Proc. Indian Acad. Sci.* **1A**, 189 (1934); *Ibid.* **2A**, 574 (1935); *Ibid:* **3A**, (1936). B. S. Rao *J. Sci. Ind. Res. India* **7**, N. 1 B, 11 (1948) (From the essential oil of leaves of *Clausena willdenovii*).

[6] H. Hondo and Yamaguchi *J. Pharm. Soc. Japan* **39**, 263 (1919); H. Kondo and H. Suzuki *Ber. Dtsch. Chem. Ges.* **69**, 2459 (1936); H. Suzuki *J. Pharm. Soc. Japan* **56**, 841 (1936); Goto *Ibid.* **57**, 77 (1937) (Isolated from the essential oil of *Perilla citriodora* Mak.).

This would suggest, from a purely formal point of view, a possible derivation of furan terpenes and sesquiterpenes from the corresponding acyclic members.

So far as the authors know, dendrolasin represents the first furan derivative ever found in the animal kingdom. It is worth noticing that structures which can be dissected into isoprene units do exist in other natural products occurring in insects. Such are: *cantharidin* $C_{10}H_{12}O_4$ (VIII), which contains a carbon atom skeleton corresponding to the tail-to-tail union of two isoprene residues*; *iridomyrmecin* $C_{10}H_{16}O_2$ (IX)[7] its epimer iso-*iridomyrmecin*,[8] and *iridodial* $C_{10}H_{16}O_2$ (X)[9] all the three with the head-to-tail structure:



VIII IX X

The isoprene rules, which have been so helpful for the interpretation of the molecular architecture of many plant products, may also be a useful guide in the still scarcely investigated field of insect chemistry.

EXPERIMENTAL

Isolation of dendrolasin (I)

The brown oily residue obtained, after removal of the solvent, from the light petroleum ether extract of the insect,[10]† was steam distilled until no oily droplets were noticeable in the condenser. The aqueous distillate was extracted with ether; distillation of the solvent left a pale yellow oil which, fractionated under reduced pressure, yielded about 75 per cent of its weight of practically pure dendrolasin, b.p. 148–150°/16 mm. Dendrolasin is a colourless liquid, with a pleasant smell of lemon grass, almost insoluble in water, optically inactive. n_D^{20} 1·4860, d_4^{23} 0·9108 (Found: C, 82·43 82·51; H, 10·31 10·35. Calc. for $C_{15}H_{22}O$: C, 82·51; H, 10·16 per cent).

The product is stable towards alkalis and readily converted into resinous products by concentrated mineral acids. Does not react with hydrazine, *p*-nitrophenylhydrazine, semicarbazide hydrochloride, phenylisocyanate and maleic anhydride. With aqueous mercuric acetate, in the presence of sodium acetate, it gives a white precipitate, insoluble in methanol and acetone, which on heating is decomposed at 205° without melting.

The colour reactions of dendrolasin and its i.r. and u.v. spectra have already been reported and discussed in the introduction to this paper.

* In cantharidin the saturated C_4O ring is also present.

† This was obtained by extracting the insects with petroleum ether, after the insect had been mixed with kieselguhr and pressed at 300 atm.

[7] R. Fusco, R. Trave and A. Vercellone *Chim. et Industr.* **37**, 351 958 (1955) (From the ant *Iridomyrmex humilis* Mayr.).

[8] G. W. K. Cavill, D.L. Ford and H. D. Locksley *Australian Chem. J.* **9**, 288 (1956); *Chem. & Ind. (Rec).* 465 (1956) (From the ant *Iridomyrmex nitidus* Mayr.).

[9] Cavill *et al., loc. cit.*; R. Trave and M. Pavan *Chim. et Industr.* **38**, 1015 (1956) (From the ants *Iridomyrmex detectus* Sm., *I. conifer.* For. and *Tapinoma nigerrimum* Nyl.).

[10] M. Pavan *Ric. Sci.* **26**, 147 (1956).

Catalytic hydrogenation of dendrolasin to perhydrodendrolasin (III)

(a) *In acetic acid solution over PtO_2.* A solution of 3 g of dendrolasin in 100 ml of glacial acetic acid was shaken with hydrogen, at ordinary pressure and room temperature, in the presence of 30 mg of PtO_2. The absorption of H_2 ceased when 1300 N ml had been fixed, amounting to 4·23 mole per mole of substance. After removal of the catalyst, the solution was treated with an excess of dilute NaOH, and the oil thus separated was extracted with ether. The dried (Na_2SO_4) ethereal layer, gave after removal of the solvent, an oily residue which was fractioned twice at reduced pressure. The hydrogenated derivative is an odourless liquid, b.p. 155°/15 mm, n_D^{20} 1·4484, which does not give the pine shaving reaction, and only a very faint pink colour on heating with HCl-ethanol solution of vanillin. The analysis was in good agreement with the required for an octahydroderivative. (Found: C, 79·16 79·20; H, 13·23 13·19. Calc. for $C_{15}H_{30}O$: C, 79·57; H, 13·36 per cent).

The i.r. spectrum of the sample prepared above, indicated the presence of traces of hydroxylated and acetylated impurities, evidently formed by reductive cleavage of the tetrahydrofuran ring.

(b) *In ethanol over Raney nickel.* 1·6 g of dendrolasin dissolved in 100 ml of ethanol, were hydrogenated at room temperature in the presence of 0·5 g of W_5 Raney nickel.[11] After 3–4 hr 657 N ml of H_2 were absorbed (4·0 mole per mole of dendrolasin). Distillation of the solvent after removal of the catalyst gave a liquid residue which distilled *in vacuo* yielded an oil n_D^{20} 1·4478. Vanillin reaction was negative.

(c) *In ethanol over Pd—C.* A solution of 5 g of dendrolasin in 100 ml of ethanol was shaken with hydrogen at the ordinary conditions in the presence of 0·2 g of Pd—C (containing 10 per cent Pd). The absorption of hydrogen (rather slow) ceased completely when 1960 N ml of H_2 had been absorbed (3·83 mole per mole of substance). After removal of the catalyst and the solvent, the oily residue was distilled under reduced pressure. B.p. 155°–157°/16 mm; 186°–187°/46 mm; n_D^{20} 1·4490. Vanillin and pine shaving reaction were negative. For the i.r. spectrum (Fig. 1, No. 3), see the introduction.

Catalytic hydrogenation of dendrolasin to tetrahydrodendrolasin

A suspension of 0·2 g of Pd—C (10 per cent Pd) and 0·2 g of Pd—$BaSO_4$ (5 per cent Pd) in 5 ml of ethanol was left overnight, then added to a solution of 2 g of dendrolasin in 100 ml of ethanol. By shaking with hydrogen at room temperature a slow absorption occurred, which ceased when 410 N ml of H_2 had been absorbed (about 2 mole per mole of substance). After removal of the catalyst and of the solvent, the residue was fractioned at reduced pressure. B.p. 160°/5 mm; n_D^{20} 1·4585 (Found: C, 80·52; H, 11·67. The tetrahydroderivative $C_{15}H_{26}O$ requires: C, 80·02; H, 11·79 per cent).

Tetrahydrodendrolasin is a colourless, faintly scented oil, which gives the pine shaving reaction and a red colour with vanillin in HCl-ethanol solution. Concentrated sulphuric acid dissolves it with red-brown colour. The i.r. spectrum is reported in Fig. 1, No. 2.

The same tetrahydroderivative could be obtained also by hydrogenation over Willstaetter platinum, using a sparingly active sample of this catalyst.* 1·2 g of

* The catalyst had been prepared as described in *Houben Methoden der org. Chemie* 3d Ed. Vol. III. p. 312, and preserved for about 1 year before using.

[11] A. A. Pavlic and H. Adkins *J. Amer. Chem. Soc.* **68**, 1471 (1946).

dendrolasin shaken in ethanolic solution (100 ml) with 0·2 g of the catalyst, absorbed 260 N ml of H_2 (2·1 mole per mole of the substance), and gave a tetrahydroderivative with n_D^{20} 1·4595.

Oxidation of dendrolasin with potassium permanganate

To a suspension of 1 g of dendrolasin in 200 ml of water contained in a flask equipped with a dropping funnel and a reflux condenser and heated on the water-bath, were added drop wise under frequent shaking 75 ml of 2 per cent $KMnO_4$ solution. After 2 hr the reaction mixture was distilled, and the first 5 ml of distillate were collected in a solution of *p*-nitrophenylhydrazine in acetic acid. The abundant yellow precipitate thus formed was recrystallised twice from hexane. Yellow needles were obtained which melted at 149°·5 and showed no m.p. depression when mixed with an authentic specimen of *acetone* p-*nitrophenylhydrazone*.

The aqueous solution, after filtration from the MnO_2 and extraction with ether to remove the unchanged dendrolasin, was concentrated to small volume on the water-bath, acidified with sulphuric acid, and again extracted with ether. Removal of the solvent gave a white crystalline residue containing some *oxalic acid* which was dissolved in a small quantity of water. This solution was then treated with dilute H_2SO_4 and an amount of permanganate solution sufficient to destroy the oxalic acid. A new extraction with ether yielded a crystalline acid which, recrystallised from water, melted at 183°–184° and was identical with *succinic acid*. The identity has been confirmed by a mixed melting point test, and from the crystalline form of the sublimated acid.

Ozonolysis of dendrolasin

0·5 g of dendrolasin dissolved in 30 ml of pure ethyl acetate were submitted for 10 hr to a slow stream of ozonised oxygen. After remaining overnight the solvent was removed *in vacuo* at room temperature, and the resulting syrup refluxed for 2 hr with 50 ml of water. The solution was then distilled, and the first 4–5 ml of liquid were collected. On standing, white, square, tabular crystals were formed, which detonated when suddenly heated, and melted at 127°–131° (crude). The product is identical with cyclo-*diacetone peroxide*,* a sample of which we prepared by ozonolysis of geraniol.

The remaining solution was made slightly alkaline with dilute NaOH, then repeatedly extracted with ether. Evaporation of the solvent left a liquid (0·1–0·15 g) endowed with a strong aldehydic odour, which was treated with a boiling solution of 2:4-dinitrophenylhydrazine in methanol. The precipitate, collected and dried, was dissolved in hot nitrobenzene. The microcrystalline orange coloured product separated on cooling, washed with boiling ethanol to remove the last traces of nitrobenzene, melted at 235°. The substance is identical with *levulinic aldehyde* bis-2:4-*dinitrophenylhydrazone*, and showed no depression at the mixed melting point test with a pure synthetic specimen[12] (Found: N, 24·50. Calc. for $C_{17}H_{16}O_8N_8$: N, 24·34 per cent).

* The formation of this substance in ozonolysis of products containing $(C)=C(CH_3)_2$ groups has been reported by several authors.

[12] H. H. Strain *J. Amer. Chem. Soc.* **57**, 760 (1935).

The aqueous alkaline solution was again acidified with sulphuric acid and extracted with ether. The residue obtained after distillation of the solvent was dissolved in water, the solution evaporated to dryness, and the solid product pressed on a porous tile to remove oily impurities. Recrystallisation from water gave 0·2 g of an acid m.p. 187°, which was identical with *succinic acid*.

Acknowledgements—We thank Dr. E. Mantica for his assistance in the interpretation of the i.r. spectra, and Dr. F. Canal of the Farmitalia Laboratory for some of the analyses contained in this paper.

Tetrahedron, 1957, Vol. 1, pp. 186–194. Pergamon Press Ltd., London

SYNTHESIS OF TETRAHYDRO- AND PERHYDRO-DENDROLASIN

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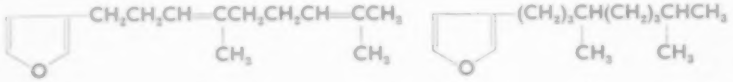
(*Received* 22 *March* 1957)

VOL. 1 1957

Abstract—Structure (I) of β-(4:8-dimethylnona-3:7-dienyl) furan assigned by the authors to *dendrolasin* on the basis of the chemical and spectrochemical evidence reported in a previous paper, has been confirmed by the synthesis of its hydroderivatives.

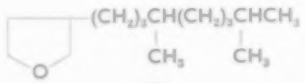
Tetrahydrodendrolasin (II) [β-(4:8-dimethylnonyl) furan] has been prepared by condensation of β-furoyl chloride with tetrahydrogeranylcadmium and subsequent Wolff-Kishner reduction of the resulting ketone (XII). *Perhydrodendrolasin* (III) [β-(4:8-dimethylnonyl) tetrahydrofuran] has been synthesised: (a) by Stobbe condensation of 4:8-dimethylnonoic aldehyde (V) with ethyl succinate, followed by reduction to 2-(4′:8′-dimethylnonyl) butandiol-1:4 (VIII) and dehydration of this last to the corresponding tetrahydrofuran derivative (III) (b) by catalytic hydrogenation of the synthetic tetrahydro-derivative (II). Synthetic tetrahydro- and perhydrodendrolasin have proved in every respect to be identical with the corresponding hydroderivatives of natural dendrolasin.

As reported in a previous paper,[1] the results of chemical investigations on *dendrolasin*, the odourous substance $C_{15}H_{22}O$ produced by the ant *Lasius* (*Dendrolasius*) *fuliginosus* Latr., had led us to assign to this product the structure of β-(4:8-*dimethylnona*-3:7-*dienyl*) *furan* (I) :



I

II



III

Formula (I), which is in excellent agreement with the i.r. spectrum data of the substance and its hydroderivatives, appeared also convincing from the biogenetic point of view, since it could be derived from the head to tail linking of three isoprene units. It was however necessary to give a direct confirmation of structure (I), and this could be achieved only through the synthesis of dendrolasin or its hydroderivatives (II) and (III).

Synthesis of β-alkylfurans has been achieved in a few cases*; considering the difficulties marking the introduction of the long unsaturated isoprenoid chain contained in dendrolasin, we decided to direct our attempts first to the preparation of its hydroderivatives.

* Only three β-alkylfurans are reported in the literature, that is: β-methyl, β-*iso*propyl and β-*iso*hexylfuran. This last (dihydroperillene) has been obtained by catalytic hydrogenation of perillene. No i.r. spectrum data of β-alkyl furans were available till now.

[1] A. Quilico, F. Piozzi, and M. Pavan *Tetrahedron* **1**, 177 (1957).

Among the different routes which could be planned for the synthesis of *perhydrodendrolasin* (III), those summarised in (A) and (B) appeared most convenient,[2*]

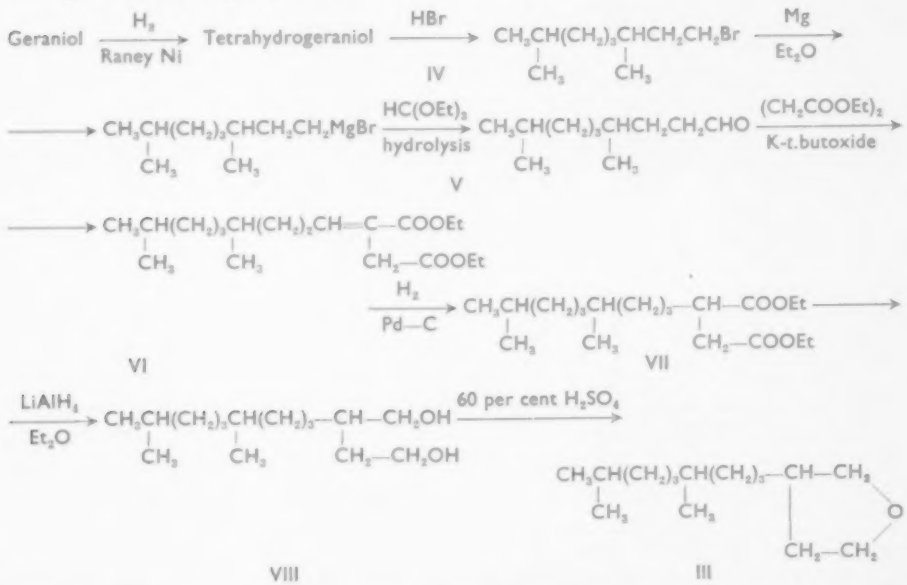
(A) Synthesis of 2-(4′:8′-dimethylnonyl)butandiol-1:4 (VIII) and subsequent cyclisation to β-(4:8-dimethylnonyl)tetrahydrofuran (III)

(B) Synthesis of β-(4:8-dimethylnonoyl)furan (XII) starting from β-furoic acid, followed by reduction to CH_2 of the CO group, and successive hydrogenation of the furan ring to tetrahydrofuran.

Tetrahydrodendrolasin (II) could be synthesised according to scheme (B) by limiting the process to the last but one stage.

Both methods (A) and (B) have been used with success. Before carrying out the syntheses with starting materials of difficult and laborious preparation such as β-furoic acid and 4:8-dimethylnonoic aldehyde required respectively by scheme (A) and (B), both processes have been tested on easily available products, in order to find the proper experimental conditions. Several models of (III), containing a simpler side chain, and some α-substituted furans (among them the α-isomer of tetrahydrodendrolasin) have been thus synthesised†.

Synthesis of *perhydrodendrolasin* (III) according to scheme (A) has been performed through the following steps:



Geraniol has been hydrogenated in ethanol solution over Raney nickel to tetrahydrogeraniol, and this has been transformed with HBr into tetrahydrogeranyl bromide (IV). The subsequent step which leads to 4:8-*dimethylnonoic aldehyde* (V) has

* Both routes had been successfully applied respectively to the synthesis of α-substituted tetrahydrofurans and furans.

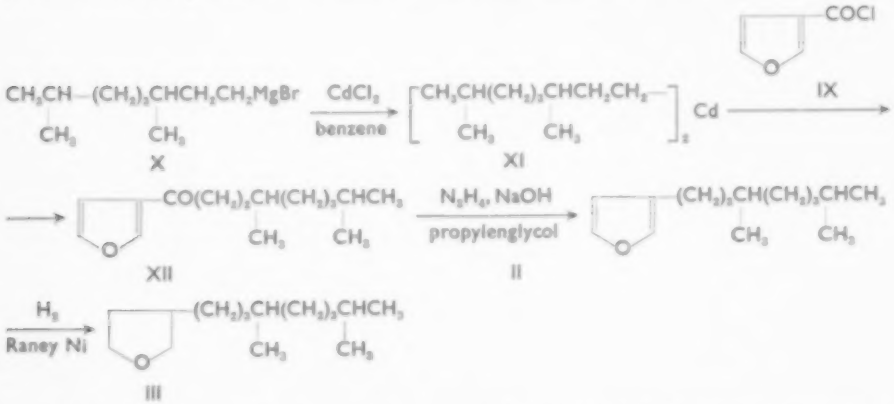
† The preparation of these compounds will be reported in a subsequent paper.

[2] W. Longinow *J. Russ. Phys. Chem. Soc.* **46**, 1084 (1914); *Ibid.* **47**, 1139 (1915); C. G. Overberger and C. W. Roberts *J. Amer. Chem. Soc.* **71**, 3618 (1949); T. Reichstein *Helv. Acta* **13**, 345 (1930); H. Gilman and N. O. Calloway *J. Amer. Chem. Soc.* **55**, 4203 (1933); N. I. Shnikin, B. V. Shemastina, and B. D. Cherkasova *J. Gen. Chem.* U.S.S.R. **8**, 674 (1938); M. Petizon and P. Baranger *C. R. Acad. Sci. Paris* **234**, 2296 (1952); *Ibid.* **236**, 499 (1953).

been achieved by condensing tetrahydrogeranylmagnesium bromide with ethyl orthoformate. The diacetal thus obtained, saponified with dilute hot sulphuric acid, gives the free aldehyde which has been purified through its bisulphite derivative. Stobbe's condensation of the aldehyde (V) with diethyl succinate afforded the diethylester (VI) of 4:8-*dimethylnonylidensuccinic acid*. The subsequent reduction of (VI) gave *diethyl* 4:8-*dimethylnonylsuccinate* (VII); this last, treated with lithium aluminium hydride in ether solution, produced in good yield 2-(4′:8′-*dimethylnonyl*)*butandiol*-1:4 (VIII). The final step of the synthesis, that is the dehydration of glycol (VIII) to the corresponding β-(4:8-*dimethylnonyl*)*tetrahydrofuran* (III) was carried out in 75 per cent yield by heating with 60 per cent sulphuric acid.

The product thus obtained is a colourless liquid b.p. 156°/15 mm, n_D^{20} 1·4488. It appears in any respect to be identical with *perhydrodendrolasin* prepared by catalytic hydrogenation of natural dendrolasin, as described in a previous paper.[1] A comparison of the i.r. spectra of the two products, as shown in Fig. 1, A, confirms their identity.

Synthesis of *tetrahydrodendrolasin* (II) and *perhydrodendrolasin* (III) starting from β-furoic acid, as planned in scheme (B), has been achieved as follows:



Tetrahydrogeranylcadmium (XI), prepared from tetrahydrogeranylmagnesium bromide (X) and anhydrous $CdCl_2$, has been condensed in benzene solution with β-furoyl chloride (IX). The Wolff-Kishner reduction of the thus obtained and properly purified β-(4:8-*dimethylnonoyl*)*furan* (XII) afforded in a fairly good yield β-(4:8-*dimethylnonyl*)*furan* (II). Synthetic tetrahydrodendrolasin (II) is a colourless liquid b.p. 90–91°/0·6 mm, n_D^{20} 1·4571 which turns slowly to brown on exposure to air and light. It gives a pine shaving test and a colour reaction with vanillin which are very similar to those of natural dendrolasin. Its physical and chemical characteristics demonstrate that it is identical with the tetrahydroderivative obtained by hydrogenation of dendrolasin over Pd—C—$BaSO_4$ under controlled conditions, as previously reported. The i.r. spectra shown in Fig. 1, D, also confirm the identity of the two products.

Hydrogenation of (II) in the presence of Raney nickel yielded a β-(4:8-dimethylnonyl)tetrahydrofuran (III), b.p. 120°/1·8 mm, n_D^{20} 1·4481, which proved to be identical with the product synthesised according to scheme (A), and with perhydrodendrolasin from natural source, as shown by the i.r. spectra reported in Fig. 1, B.

Although the synthesis of perhydrodendrolasin according to scheme (B) might

appear more simple and direct than that achieved following the alternative route (A), it has proved to be in practice rather toilsome, because of the intervention of secondary reactions which lead to undesired by-products very difficult to eliminate. Such are: (a) *tetrahydrogeranyl β-furoate*, which always is formed in conjunction with ketone

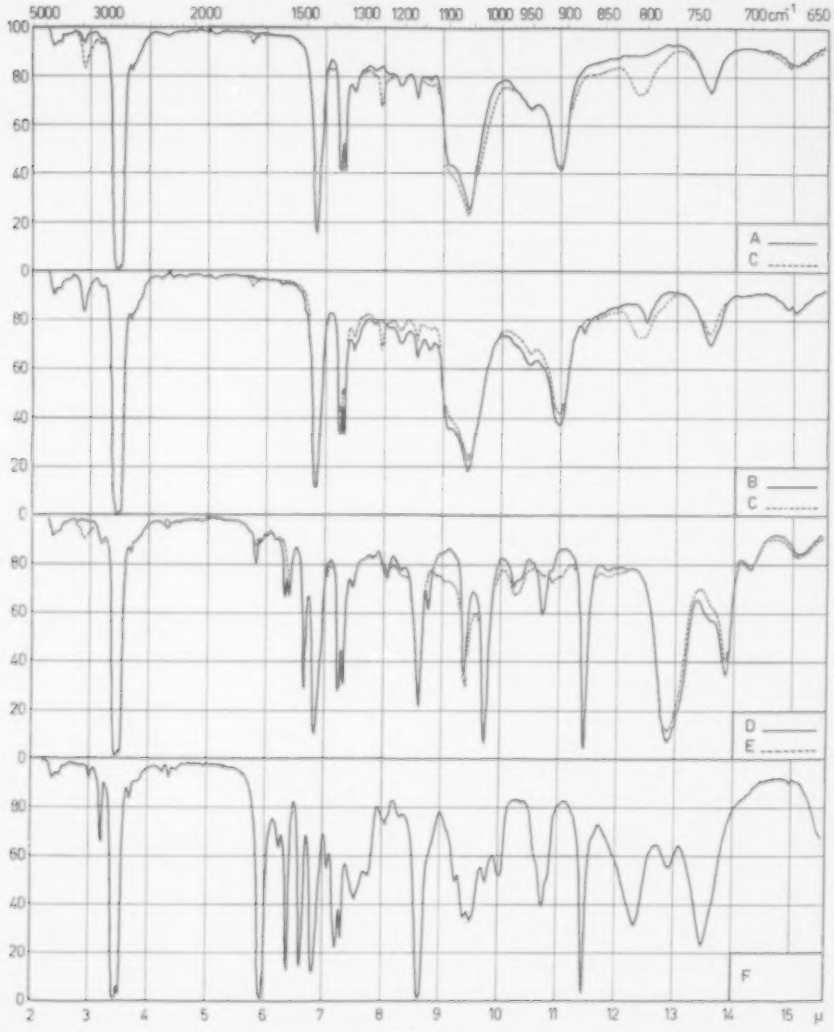


FIG. 1. Infra-red spectra
A synthetic β-(4:8-dimethylnonyl)tetrahydrofuran, via glycol, liquid 0·023 mm
B synthetic β-(4:8-dimethylnonyl)tetrahydrofuran, via β-furoic acid, liquid 0·0264 mm
C Perhydrodendrolasin, liquid 0·022 mm
D synthetic β-(4:8-dimethylnonyl)furan, liquid 0·0264 mm
E Tetrahydrodendrolasin, liquid 0·0263 mm
F β-(4:8-dimethylnonoyl)furan, liquid 0·0247 mm

(XII) in the reaction between tetrahydrogeranylcadmium and β-furoyl chloride, even when pure tetrahydrogeranyl bromide completely free from the corresponding alcohol had been employed, and (b) 2:6:11:15-*tetramethylhexadecane* (crocetane), which is

formed in the action of magnesium on the bromide. i.r. spectrum have proved very helpful in this work for testing the purity of the reagents and for the identification of the secondary products formed in the different stages of the synthesis.

The above described syntheses of tetrahydro- and perhydro-dendrolasin confirm that the structure we had assigned to dendrolasin on the basis of chemical and spectrochemical evidences is correct.

EXPERIMENTAL

Preparation and purification of tetrahydrogeranyl bromide. Commercial geraniol was carefully fractionated at ordinary pressure, and the 225–230° fraction submitted to catalytic hydrogenation in ethanol solution at 120° and 50–80 atm pressure over Raney nickel W5. The product thus obtained gave on fractionation at reduced pressure pure tetrahydrogeraniol with b.p. 114–115°/17 mm, and n_D^{20} 1·4407, in agreement with the data recorded in the literature.[3] Yield 80 per cent.

A mixture of 100 g of tetrahydrogeraniol and 200 ml HBr *d* 1·48 was refluxed for 6 hr under vigorous mechanical stirring. The oily layer was washed with Na_2CO_3 solution, dried (Na_2SO_4), and then distilled *in vacuo*. The resulting tetrahydrogeranyl bromide, obtained in 75 per cent yield, boiled at 107°/18 mm; $n_D^{20.5}$ 1·4528. Although its physical constants were in agreement with those assigned by literature to the pure bromide,[4] the i.r. spectrum of the product thus obtained indicated that about 5–8 per cent of the unchanged alcohol was still present. This was eliminated by treating the bromide with twice the amount of 4-nitrobenzoyl chloride required for complete esterification of the free alcohol, and the equivalent quantity of anhydrous pyridin. The mixture was heated for about 30 min, then the solid products were discarded and the liquid was fractionated twice at reduced pressure. Pure tetrahydrogeranyl bromide free from tetrahydrogeraniol (no OH bands in its i.r. spectrum) has the following physical constants: b.p. 75–76°/1 mm; n_D^{20} 1·4537.

β-Furoyl chloride was prepared by refluxing β-furoic acid with thionyl chloride in benzene solution, as reported in the literature.[5] The product we used boiled at 78–80°/55 mm and melted at 27°.

Preparation of 4:8-dimethylnonoic aldehyde. This compound has already been reported in the literature.[6] More convenient, for preparative purposes, is the procedure we have elaborated as follows. In a dry 1 l. four-necked flask, equipped with a Hershberg stirrer,[7] a reflux condenser, a dropping funnel and a nitrogen inlet tube, were introduced 6·1 g (0·254 g atoms) of magnesium turnings and 60 ml of anhydrous ether. About the tenth part of a solution of 56 ml (0·254 mole) of pure tetrahydrogeranyl bromide in 125 ml of ether was then added through the funnel. The reaction was initiated by the addition of a few crystals of iodine and the remainder of the bromide introduced over a period of about 1½ hr under continual stirring. The reaction mixture was then refluxed on the water-bath for 1 hr and 33·15 g (0·233 mole) of freshly distilled ethyl orthoformate were added dropwise under constant stirring. After the addition of the orthoformate, the reaction was completed by refluxing on the water-bath for 4 hr. The reaction mixture was then cooled and cautiously decomposed

[3] S. Natelson, S. Gottfried, and S. Kornblau *J. Amer. Chem. Soc.* **64**, 1484 (1942).
[4] J. v. Braun and W. Kaiser *Ber. Dtsch. Chem. Ges.* **56**, 2272 (1923).
[5] H. Gilman and R. R. Burtner *J. Amer. Chem. Soc.* **55**, 2905 (1933).
[6] J. v. Braun and W. Kaiser *loc. cit.*; F. G. Fisher and K. Loewenberg *Liebigs Ann.* **475**, 201 (1929); I. Heilbron and A. Thompson *Soc.* 892, (1929).
[7] *Organic Syntheses* Coll. Vol. 2, p. 117.

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with ice and dilute HCl. The organic layer thus separated, dried (Na_2SO_4), left after removal of the solvent the diethylacetal of 4:8-dimethylnonoic aldehyde. The hydrolysis of this last was carried out by refluxing for 1 hr with dilute H_2SO_4, taking up into ether the aldehyde set free. The crude aldehyde left after elimination of the solvent had a b.p. 84–87°/2 mm, and contained traces of halogenated products; it was therefore purified through its bisulphite derivative. For this purpose 33·5 g of aldehyde were added to the clear solution obtained by mixing 40 ml of a saturated $NaHSO_3$ solution with 40 ml of methanol, and the mixture was shaken for 6 hr in a well stoppered bottle. The white crystalline precipitate was collected, washed with methanol and ether, and then decomposed with a suspension of 10 g of $NaHCO_3$ in 80 ml of water. The aldehyde was isolated from the mixture by steam distillation, followed by extraction with ether and fractionation *in vacuo* (in the presence of trace of hydroquinone) of the oily residue left after removal of the solvent. The pure 4:8-dimethylnonoic aldehyde thus obtained weighed 7·6 g (17·5 per cent yield). It is a colourless liquid endowed with a peculiar smell, soluble in most of organic solvents. B.p. 75–76°/0·8 mm, n_D^{20} 1·4301.

Synthesis of Perhydrodendrolasin According to Scheme A

Condensation of 4:8-*dimethylnonoic aldehyde* (*V*) *with diethyl succinate : diethyl ester of* 4:8-*dimethylnonylidensuccinic acid* (*VI*).[8] To 250 ml of anhydrous *tert*-butanol contained in a ½ l. flask fitted with a reflux condenser, a dropping funnel and a nitrogen inlet tube, 8·7 g of metallic potassium were added, maintaining a continuous slow stream of nitrogen. A mixture of 44 g of diethyl succinate and 34·4 g of 4:8-dimethylnonoic aldehyde was then added to the boiling potassium-alkoxide solution, and the whole was refluxed for 24 hr in nitrogen atmosphere. After removal of the greatest part of the *tert*-butyl alcohol by distillation at reduced pressure, the reaction mixture was made slightly acidic with dilute HCl, and the remainder of the solvent removed by steam distillation. The mixture was then extracted with ether, and the extract repeatedly washed with 10 per cent Na_2CO_3 solution; the organic layer, containing some diethyl succinate was discarded. The aqueous alkaline layer, acidified with HCl and extracted with ether gave, after removal of the solvent, a brownish oil which was dissolved in ten times its volume of absolute ethanol. This solution was saturated with dry gaseous HCl, and kept at room temperature for 24 hr. After removing the HCl and the ethanol at reduced pressure, the residue was poured into ice water and extracted with ether. The ether layer, washed with Na_2CO_3 and dried (Na_2SO_4), gave a residue which was fractionated *in vacuo*. At 160°/2·5 mm diethyl succinate was recovered then, at 171–173°/2·5 mm, diethyl dimethylnonylidensuccinate distilled as a viscous oil n_D^{20} 1·4536. Yield 24 per cent (Found: C, 69·85; H, 10·54. Calc. for $C_{19}H_{34}O_4$: C, 69·90; H, 10·50 per cent).

Catalytic hydrogenation of diethyl dimethylnonylidensuccinate: diethyl ester of 4:8-*dimethylnonylsuccinic acid* (VII). 22 g of the above described diethylester, dissolved in 100 ml of ethanol, were shaken with hydrogen at room temperature and at 3 atm pressure in the presence of 0·2 g of Pd—C. The H_2 absorption was completed in 3–4 hr. After filtration of the catalyst and removal of the solvent, the residue was distilled at reduced pressure. Diethyl 4:8-dimethylnonylsuccinate is a colourless oil

[8] G. C. Overberger and C. W. Roberts *loc. cit.*

b.p. 175–176°/4 mm with n_D^{20} 1·4404. Yield 80 per cent. (Found: C, 69·29; H, 10·73. Calc. for $C_{19}H_{36}O_4$: C, 69·47; H, 11·05 per cent.)

Reduction of diethyl dimethylnonylsuccinate with lithium aluminium hydride; 2-(4′:8′-*dimethylnonyl*)*butandiol*-1:4 (VIII). A solution of 16·7 g of the ester in 200 ml of dry ether was refluxed with 3·8 g of $LiAlH_4$ at the water-bath for a period of 6 hr. The unaffected hydride was then decomposed with moist ether and water. The organic layer, dried (Na_2SO_4) and distilled, gave a residue which was fractionated at reduced pressure. At 159–160°/0·12 mm the glycol distilled as a viscous liquid with n_D^{20} 1·4588. Yield 10 g (about 80 per cent of the theoretical amount).

Dehydration of dimethylnonylbutandiol to β-(4:8-*dimethylnonyl*)*tetrahydrofuran* (*synthetic perhydrodendrolasin*) (III). The procedure described by Longinow[9] for the conversion of 1:4-glycols into the corresponding tetrahydrofurans has been employed. A mixture of 8·9 g of dimethylnonylbutandiol and 20 ml of 60 per cent (by weight) sulphuric acid was heated in a 50 ml distillation flask under reduced pressure (200 mm); a colourless emulsion was formed which gradually turned brown. The temperature was then allowed to rise to the boiling point of the mixture, and held at this point until 10 ml of distillate (which separated into two layers) were collected. The dark reaction mixture left in the distillation flask was diluted with water, made slightly alkaline and then extracted with ether. The solvent was removed and the residue steam distilled. The aqueous distillate thus obtained, combined with the portion collected during the first phase of the reaction, was again taken up into ether. Distillation of the ether solution, previously washed with Na_2CO_3, gave an oily residue which was fractionated at reduced pressure. At 156°/15 mm the β-dimethylnonyltetrahydrofuran distilled as a colourless liquid of faint odour, n_D^{20} 1·4488. Yield 6 g (about 75 per cent) (Found: C, 79·26; H, 12·98. Calc. for $C_{15}H_{30}O$: C, 79·57; H, 13·36 per cent). The i.r. spectrum of the thus prepared perhydro-dendrolasin is given in Fig. 1, A. It is practically identical with that of the product prepared by hydrogenation of dendrolasin.

Synthesis of tetrahydrodendrolasin and perhydrodendrolasin according to scheme B.

Synthesis of β-(4:8-*dimethylnonoyl*)*furan* (XII).[10] A solution of tetrahydrogeranylmagnesium bromide was prepared as described (p. 190), starting from 56 ml (0·254 mole) of pure tetrahydrogeranyl bromide, 6·1 g (0·254 g atom) of Mg turnings and 125 ml of anhydrous ether. Titration with N/10 H_2SO_4 and NaOH indicated that the Grignard reagent had been formed in a 86·5 per cent yield. To the cool, clear solution of the Grignard 23·6 g (0·127 mole) of recently melted anhydrous cadmium chloride were added over a period of 5–10 min. After all the $CdCl_2$ had been introduced, the mixture was stirred and heated under reflux until the Gilman test for unchanged Grignard reagent was negative (about 20 min were required). Ether was then rapidly distilled from the reaction mixture until a semisolid residue was left; at this point 80 ml of pure dry benzene were introduced, and the distillation was continued until 60 ml of the solvent were collected. An additional 70 ml portion of benzene was then added and, with continual stirring, a solution of 27 g (0·207 mole) of β-furoyl chloride in 60 ml of benzene was dropwise added at room temperature. After refluxing for about 1 hr, the reaction mixture was cooled and decomposed with ice and dilute sulphuric acid. The benzene layer was separated and the aqueous phase extracted with ether.

[9] *loc. cit.*
[10] D. A. Shirley *Org. React.* VIII 28 (1954).

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The combined organic extracts, washed with $NaHCO_3$ solution and dried (Na_2SO_4), were evaporated. The oily, reddish coloured residue, fractionated at reduced pressure gave a small quantity of unchanged furoyl chloride and 37·3 g of crude ketone b.p. 150–160°/8–9 mm. Yield 76.5 per cent.

The product thus obtained contained some *tetrahydrogeranyl β-furoate* and some *crocetane* (2,6:11:15-tetramethylhexadecane) which could not be removed by distillation. The i.r. spectrum of an apparently pure specimen with b.p. 127·5°/0·5 mm and n_D^{20} 1·4631 prepared by repeated fractionation of the crude ketone, still showed the bands of the ester. To eliminate this last, the raw ketone was refluxed for 2 hr with 7 g of KOH in 100 ml of methanol. After distillation of the methanol, the residue was treated with water and the oil taken up into ether. Fractionation under reduced pressure of the oil recovered from the ether solution gave 5·7 g of tetrahydrogeraniol b.p. 75–85°/1 mm, $n_D^{20·5}$ 1·4437, and 27·2 g of a fraction b.p. 120–130°/1 mm with $n_D^{20·5}$ 1·4660. Some β-furoic acid (3·1 g) m.p. 121–122° was recovered from the aqueous alkaline phase by treatment with sulphuric acid. The high boiling fraction redistilled twice yielded 21·3 g of a colourless oil b.p. 140°/2·4 mm, $n_D^{20·5}$ 1·4667. The analysis and the i.r. spectrum indicated that this product contained about 25 per cent of crocetane.

The pure ketone was isolated from this mixture by converting it into the corresponding *phenylsemicarbazone*. 4·3 g of the product b.p. 140°/2·4 mm, dissolved in methanol and treated with 3·4 g of phenylsemicarbazide chloride and 1·65 g of $NaHCO_3$ gave, after 24 hr standing, 2·8 g of crystalline phenylsemicarbazone. Purified by recrystallisation from methanol it formed thin needles m.p. 125° (Found: N, 11·12 11·20. Calc. for $C_{22}H_{31}O_2N_3$: N, 11·37 per cent).

Pure dimethylnonoylfuran, set free from its phenylsemicarbazone by hydrolysis with boiling dilute H_2SO_4, is a colourless oil b.p. 115–116°/0·05 mm, n_D^{20} 1·4747 (Found: C, 76·07; H, 10·08. Calc. for $C_{15}H_{24}O_2$: C, 76·22; H, 10·24 per cent). It gives the vanillin reaction (brown-red) and the pine shaving reaction. Its i.r. spectrum is given in Fig. 1, F. Besides the strong CO band at 1685 cm^{-1} and the *iso*propyl group bands at 1384 and 1367 cm^{-1}, the following bands assignable to the furan system are present: 1565 and 1512 cm^{-1} (conjugated furan); 1158 873 and 741 cm^{-1} (β-substituted furan).

Dimethylnonoylfuran 2:4-*dinitrophenylhydrazone* crystallises from glacial acetic acid in orange needles m.p. 98–99° (Found: N, 13·52; Calc. for $C_{21}H_{28}O_5N_4$: N, 13·45 per cent). Both the *p*-nitrophenylhydrazone and semicarbazone were oils at ordinary temperature.

Wolff-Kishner reduction of dimethylnonylfuran: *β-(4:8-dimethylnonyl)furan* (*synthetic tetrahydrodendrolasin*) (II).[11] A mixture of 15 g of the ketone (purified through its phenylsemicarbazone as described) 8·6 g of NaOH, 9·5 ml of hydrazine hydrate and 130 ml of propylene glycol, was refluxed for 1 hr in nitrogen atmosphere (temperature of the liquid 146°). A portion of the liquid was then distilled until the b.p. of the reaction mixture attained 180°. After two additional hours of refluxing the mixture was poured into an excess of dilute sulphuric acid, and the oily product thus separated was extracted with ether. The portion which distilled between 146° and 180° was submitted to the same treatment. The combined extracts were washed with dilute H_2SO_4, then with water, and finally dried (Na_2SO_4). By distilling the ether solution an

[11] Huang-Minlon *J. Amer. Chem. Soc.* **68**, 2487 (1946).

oily residue was obtained which, on distillation *in vacuo*, gave 8 g of crude dimethylnonylfuran b.p. 97–102°/1·2 mm. This was purified by careful twice repeated fractionation at reduced pressure. Pure dimethylnonylfuran is a colourless oil b.p. 90–91°/0·6 mm, n_D^{20} 1·4571, which slowly turns brown on exposure to air and light (Found: C, 81·03; H, 12·34. Calc. for $C_{15}H_{26}O$: C, 81·02; H, 11·79 per cent). With vanillin in ethanol-HCl solution it gives a fine fuchsia-red colour which turns brown on heating; the pine shaving reaction is the same as that of dendrolasin (dirty blue-green).

The i.r. spectrum, reported in Fig. 1, D, is practically identical with that of the tetrahydroderivative obtained by catalytic hydrogenation of dendrolasin (Fig. 1, E).

Hydrogenation of dimethylnonylfuran with Raney nickel; β-(4:8-dimethylnonyl) tetrahydrofuran (III) (Synthetic perhydrodendrolasin). A solution of 1·85 g of synthetic tetrahydrodendrolasin in 100 ml of 95 per cent ethanol was shaken with hydrogen at room temperature and at ordinary pressure, in the presence of 2 g of Raney nickel W 5. The absorption ceased when 402 ml of H_2 (at 17° and 750 mm) had been fixed (calc. for two double bonds: 399 ml). After removal of the catalyst and the solvent, the liquid residue was distilled at reduced pressure. It yielded a colourless oil b.p. 120°/1·8 mm, n_D^{20} 1·4481. The i.r. spectrum, given in Fig. 1, B, is identical with that of perhydrodendrolasin from natural source or synthesised according to scheme A.

The authors are indebted to Dr. F. Canal of the Farmitalia Research Laboratory for some of the C,H determinations, and to Dr. E. Mantica for his assistance in the interpretation of the i.r. spectra.

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Tetrahedron, 1957, Vol. 1, pp. 195–200. Pergamon Press Ltd., London

VORSCHLAG ZUR BIOGENESE DER AMARYLLIDACEENALKALOIDE

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(*Received* 9 *April* 1957)

Abstract—A scheme is proposed for the biogenesis of the Amaryllidaceae alkaloids which involves the condensation between an aliphatic and an aromatic precursor. The hydro-aromatic nature of the C-ring of the lycorine group can thus be readily accounted for.

DIE Amaryllidaceen bilden eine Anzahl chemisch wie pharmakologisch interessanter Alkaloide, die wenig Beziehungen zu anderen Naturstoffen aufweisen. Sie enthalten fast alle ein charakteristisches hydriertes Indolinsystem neben einer partiell hydrierten Diphenyleinheit. Nach den bis heute vorgeschlagenen Strukturformeln lassen sich die Amaryllidaceenalkaloide in vier Gruppen einteilen, die im folgenden nach dem zuerst strukturaufgeklärten Alkaloid jeder Gruppe benannt werden sollen:

Lycorin- Lycorenin-, Tazettin-, Crinin- und Galanthamingruppe.

Ausgehend von der besonderen Rolle, die Dioxyphenylalanin bei der Biogenese verschiedener Alkaloidklassen spielt, wurde 1953 von Wenkert ein Biogeneseschema vorgeschlagen, das die Entstehung der Amaryllidaceenalkaloide durch oxydative Verknüpfung von 3, 4-Dioxyphenyläthylamin und 3, 4-Dioxyacetaldehyd annimmt.[1,2] Trotz seiner Einfachheit hat es den Nachteil, daß es die Bildung des hydroaromatischen Ringes C der Lycoringruppe aus einem aromatischen System nur schwer erklärt.[3,4,5]

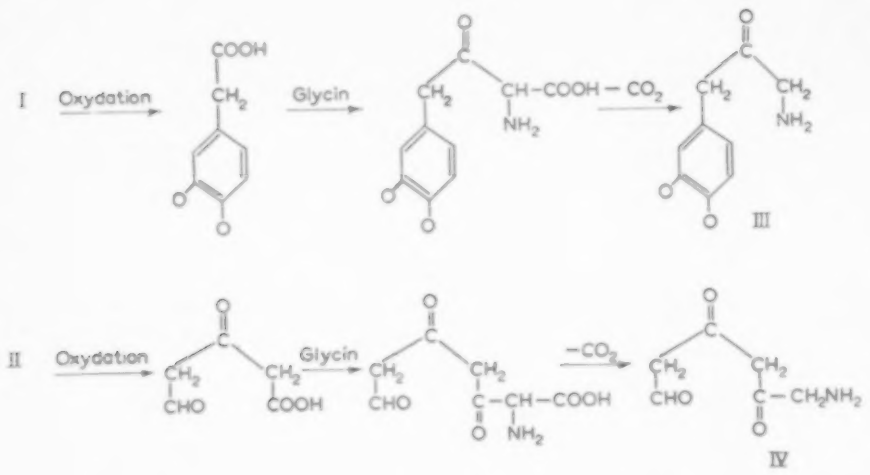
Diese Schwierigkeit läßt sich umgehen, wenn man sich die Alkaloide durch Kondensation einer Dioxyphenylalanineinheit mit einem aliphatischen Teilstück entstanden denkt. Es lassen sich dann auf einfache Weise die Strukturtypen der bis heute bekannten Amaryllidaceenalkaloide ableiten.

Der im folgenden angegebene Weg soll das Prinzip des gemeinsamen Aufbaus der verschiedenen Alkaloidgruppen erläutern.

Als Grundbausteine der Amaryllidaceenalkaloide werden 3, 4-Dioxyphenylacetaldehyd (I), β-Ketoglutardialdehyd (II) und Glycin, bzw. deren biogenetische Äquivalente angenommen. (I) und (II) sind schon wiederholt als Grundelemente verschiedener Alkaloidklassen postuliert worden.[1,6] Sie leiten sich auf einfache Weise vom 3, 4-Dioxyphenylalanin bzw. von der γ-Keto-α, α'-diaminopimelinsäure

[1] E. Wenkert *Chem. and Ind.* (*Rev.*) 1088 (1953).
[2] E. Wenkert und J. H. Hansen *Chem. and Ind.* (*Rev.*) 1262 (1954).
[3] R. Robinson *Chem. and Ind.* (*Rev.*) 1317 (1953).
[4] R. Robinson *The Structural Relations of Natural Products* p. 91. Clarendon Press, Oxford (1955).
[5] S. Takagi, W. I. Taylor, S. Uyeo, und H. Yajima *J. Chem. Soc.* 4005 (1955).
[6] R. Robinson *The Structural Relations of Natural Products* pp. 51, 67, 75, 77. Clarendon Press, Oxford (1955).

ab. Durch Kondensation der (I) und (II) entsprechenden Karbonsäuren mit Glycin könnten sich die Aminoketone (III) und (IV) bilden:



Ähnliche Kondensationen treten z. B. bei der Biosynthese der δ-Aminolävulinsäure[7] und bei Robinsons Vorschlag für die Lysergsäurebiogenese auf.[8] Durch wechselseitige Kondensationen zwischen (I) und (IV) bzw. (II) und (III) lassen sich die Grundskelette der Amaryllidaceenalkaloide ableiten.

Diese Reaktionen könnten analog anderen Alkaloidsynthesen auch *in vitro* unter zellmöglichen Bedingungen verlaufen. Es mag hier erwähnt werden, daß man sich die Kondensationsprodukte auch aus anderen Teilstücken entstanden denken kann. Es ergeben sich dadurch jedoch keine vom beschriebenen Weg grundsätzlich abweichende Reaktionsfolgen.

Die eigentlichen Alkaloide können aus den Kondensationsprodukten durch eine Reihe einfacher chemischer Umwandlungen entstehen. Im einzelnen lassen sich dabei folgende Reaktionen feststellen:

(a) Kondensation des Benzolkerns mit Formaldehyd in α-Stellung zur Seitenkette,

(b) Reduktion der Carbonylgruppe im hydroaromatischen Sechsring zur Hydroxylgruppe,

(c) Abspaltung von Wasser unter Bildung eines α, β-ungesättigten Carbonylsystems,

(d) Reduktion der Carbonylgruppe in β-Stellung zum Stickstoffatom zur Methylengruppe,

(e) Hydroxylierung in Allylstellung,

(f) Methylierung von Hydroxy- und Amino-gruppen.

[7] D. Shemin und C. S. Russell *J. Amer. Chem. Soc.* **75**, 4873 (1953); A. Neuberger und J. J. Scott *Nature, Lond.* **172**, 1093 (1953), und vorhergehende Veröffentlichungen.
[8] R. Robinson *The structural Relations of Natural Products* p. 107. Clarendon Press, Oxford (1955).

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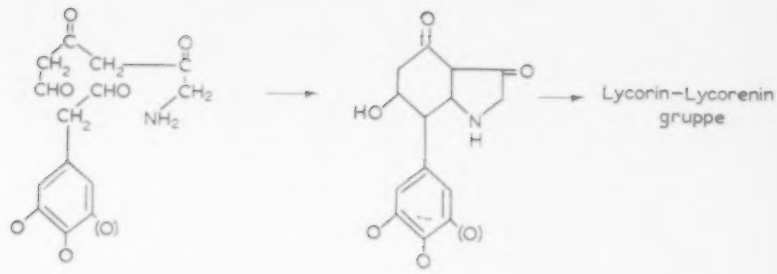
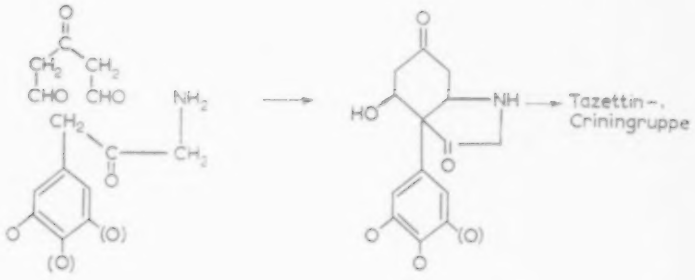
(a)

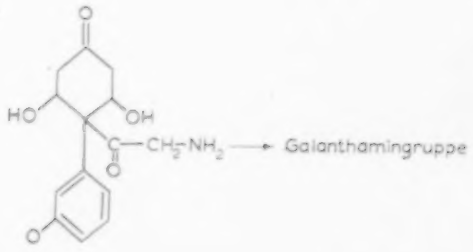

Lycorin–Lycorenin
gruppe

V

(b)

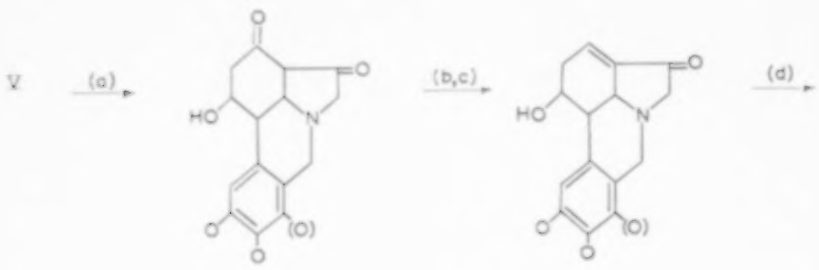

Tazettin–,
Criningruppe

VI


Galanthamingruppe

VII

Die folgenden Beispiele zeigen die Anwendung der Reaktionen (a-f) bei der Umwandlung der Primärkondensate in die natürlichen Alkaloide. Die Reihenfolge der Reaktionen läßt sich in den meisten Fällen verändern.



Caranin — Lycorin

Oxydation (f)

Lycorenin

Oxydation

Homolycorin

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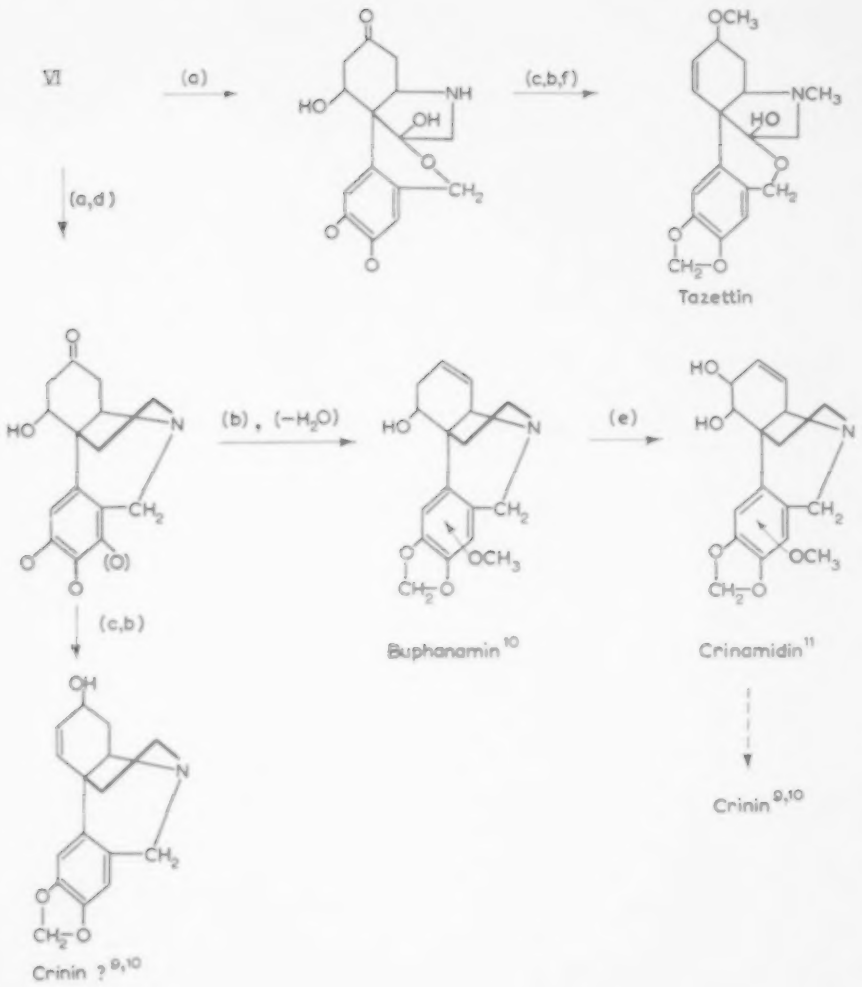
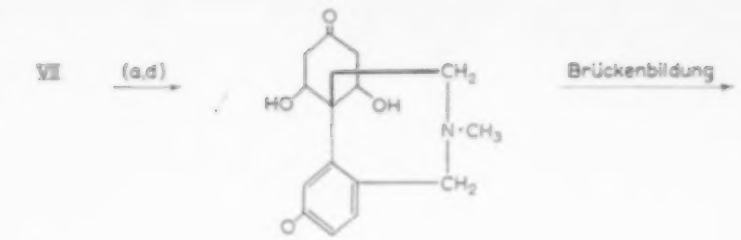
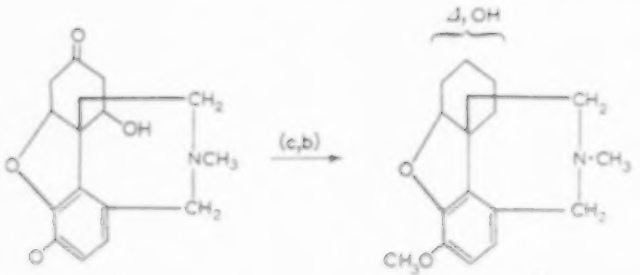


[9] W. C. Wildman *J. Amer. Chem. Soc.* **78**, 4180 (1956).
[10] W. C. Wildman *Chem. and Ind. (Rev.)* 1090 (1956).
[11] H. G. Boit und H. Ehmke *Ber. Dtsch. Chem. Ges.* **90**, 369 (1957).





Galanthamin[12]

Die angeführten Beispiele zeigen, daß man sich die Grundgerüste der bis jetzt strukturaufgeklärten Amaryllidaceenalkaloide durch Kondensation eines aliphatischen und eines aromatischen Teilstückes entstanden denken kann. Dadurch wird die hydroaromatische Natur des Ringes C der Lycorin-Lycoreningruppe ohne weiteres erklärt. Die Lage der funktionellen Gruppen läßt sich durch einfache Umformungen aus den Kondensationsprodukten (V), (VI), (VII) ableiten. Eine Ausnahme bilden evtl. einige Alkaloide der Criningruppe, deren genaue Konstitution jedoch noch nicht völlig feststeht.[9,10]

Zur besseren Übersichtlichkeit wurde hier, wie in den übrigen Formeln auf eine genauere Beschreibung der Substituenten des Benzolkerns verzichtet. Die angeführten Alkaloide dienen nur als Beispiele für den jeweiligen Strukturtyp.

[12] S. Kobayashi, T. Shingu, und S. Uyeo *Chem. and Ind. (Rev.)* 177 (1956).

Tetrahedron, 1957, Vol. 1, pp. 201–213. Pergamon Press Ltd., London

THE PREPARATION AND PROPERTIES OF SUBSTITUTED BENZO[*c*]PYRAZOLO[1:2-*a*]PYRAZOL-1:9-DIONES (MICHAELIS' BENZO-BIS-PYRAZOLONES)

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(*Received* 14 *May* 1957)

Abstract—A series of substituted benzo[*c*]pyrazolo[1:2-*a*]pyrazol-1:9-diones has been prepared by condensing β-ketoesters with β-acetyl-(2-carboxyphenyl-) hydrazine, using phosphorus trichloride as condensing agent.

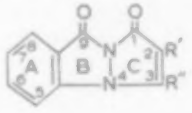
These substances are converted by (i) aqueous sodium hydroxide into substituted 1-(*o*-carboxyphenyl) pyrazol-3-ones, (ii) alcoholic solutions of sodium hydroxide into substituted 1-(*o*-alkoxycarbonylphenyl) pyrazol-3-ones, and (iii) a methanolic solution of piperidine into a mixture of 1-(*o*-methoxycarbonyl-phenylpyrazol-3-ones and the corresponding piperidide.

The titration curves of the acids in ethanolic solution with sodium hydroxide and of the bases in glacial acetic acid with perchloric acid have been recorded. From the latter the pK'_B-values of the acids and esters have been estimated.

The u.v.-absorption curves of the substances prepared have been recorded.

The preparation of β,β-diacetyl-(*o*-carboxyphenyl)-hydrazine and of 1-acetylbenzopyrazol-3-one is mentioned.

MICHAELIS[1] investigated the reaction between *o*-carboxyphenylhydrazine and ethyl acetoacetate and found that in addition to pyrazol-5-one formation (which in this instance was accompanied by a further dehydration) an anhydride of the isomeric pyrazol-3-one was formed at a higher temperature during the reaction. Michaelis assigned the name benzo-5-methyl-bis-pyrazolone to the anhydride and later[2] proved its structure by an independent synthesis. In accordance with present nomenclature this is now named 3-methyl-benzo[*c*]pyrazolo[1:2-*a*]pyrazol-1:9-dione I.



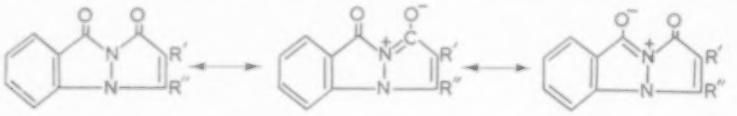
I; R'=H, R''=Me
II; R'=Et, R''=Me
III; R'=H, R''=Ph

Syntheses of I, II and III have now been achieved by condensation of β-acetyl-*o*-carboxyphenylhydrazine with ethyl acetoacetate, ethyl α-ethylacetoacetate and ethyl benzoylacetate respectively in phosphorus trichloride. All three substances form yellow crystals and their solutions in glacial acetic acid or ethanol show a very brilliant blue fluorescence.

Veibel *et al.*[3,4] have shown that 3-pyrazolones may be titrated in ethanolic solution with sodium hydroxide and in glacial acetic acid solution with perchloric acid. The substances investigated here, however, can be titrated neither as acids nor as bases.

[1] A. Michaelis *Liebigs Ann.* **373**, 148 (1910).
[2] A. Michaelis *Liebigs Ann.* **373**, 202 (1910).
[3] S. Veibel, J. Kjær, and E. Plejl *Acta Chem. Scand.* **5**, 1283 (1951).
[4] S. Veibel, K. Eggersen, and S. Linholt *Acta Chem. Scand.* **6**, 1066 (1952).

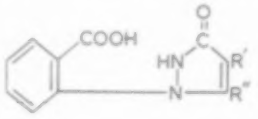
Their shortcomings as acids are easily understood, remembering that it is the enolised form of the pyrazolone which is titrated and realising that the lactimisation of the primarily formed *o*-carboxyphenyl pyrazol-3-one prohibits the enolisation. The pyrazolones may be titrated as bases when they are able to acquire a pyrazole structure or a 3-antipyrine structure IV or V. The participation of the structure I in the resonance hybride may perhaps reduce its reactivity in this titration. The resonance



between IV and V may be responsible for the fluorescence of the substances.

I may be regarded as having a 3-antipyrine structure, but only such antipyrines which have a hydrogen atom or an alkyl group on N^2 can be titrated, and here the hydrogen atom at N^2 is substituted by a benzoyl group which will certainly decrease the ability of N^2 to capture a proton so that the substance becomes almost non-basic.

Treated with aqueous sodium hydroxide the substances I–III, as indicated for I by Michaelis,[2] are converted into salts of 5-mono- or 4:5-disubstituted 1-(*o*-carboxyphenyl)pyrazol-3-ones from which the free acids VI–VIII may be liberated by addition



VI; $R' = H$, $R'' = CH_3$
VII; $R' = C_2H_5$, $R'' = CH_3$
VIII; $R' = H$, $R'' = C_6H_5$

of hydrochloric acid. The fluorescence vanishes during the opening of ring B. The acids VI–VIII on heating above their melting points lose water with ring closure to give I–III.

When titrated in ethanolic solution with sodium hydroxide VI–VIII behave as dibasic acids. When the titration is carried out electrometrically it is seen that the first jump of potential is similar to the jump generally found for carboxyphenylhydrazones,[5] the second jump is similar to the jump found for pyrazol-3-ones.[3] This is a difference from 1-(*p*-carboxyphenyl)-3-methylpyrazol-5-one which is titrated as a dibasic acid, the first jump of potential being only a hardly observable inflexion point on the titration curve.[6] The titration curves are seen in Fig. 1.

Glacial acetic acid solutions of VI–VIII may be titrated with perchloric acid in the same solvent. Fig. 2 shows the titration curves from which is estimated[4] that pK_B of the three substances are 12·2, 12·2 and 12·5 respectively, as compared with the pK_B values 12·2, 12·3 and 12·4 respectively for the corresponding 1-phenylsubstituted pyrazol-3-ones.[7] The introduction of a carboxyl group in place of a hydrogen atom in the phenyl-nucleus has evidently no significant effect on the basic properties of the pyrazolones.

When dilute sodium hydroxide is added slowly to ethanolic solutions or suspensions of I–III it is seen that the fluorescence vanishes when one equivalent of sodium hydroxide has been added. By addition of one equivalent of acid and evaporation of the solution *in vacuo* three substances may be isolated which are not the acids VI–VIII

[5] S. Veibel and H. W. Schmidt *Acta Chem. Scand.* **2**, 545 (1948).
[6] S. Veibel *Acta Chem. Scand.* **1**, 54 (1947).
[7] S. Veibel, K. Eggersen, and S. Linholt *Acta Chem. Scand.* **8**, 768 (1954).

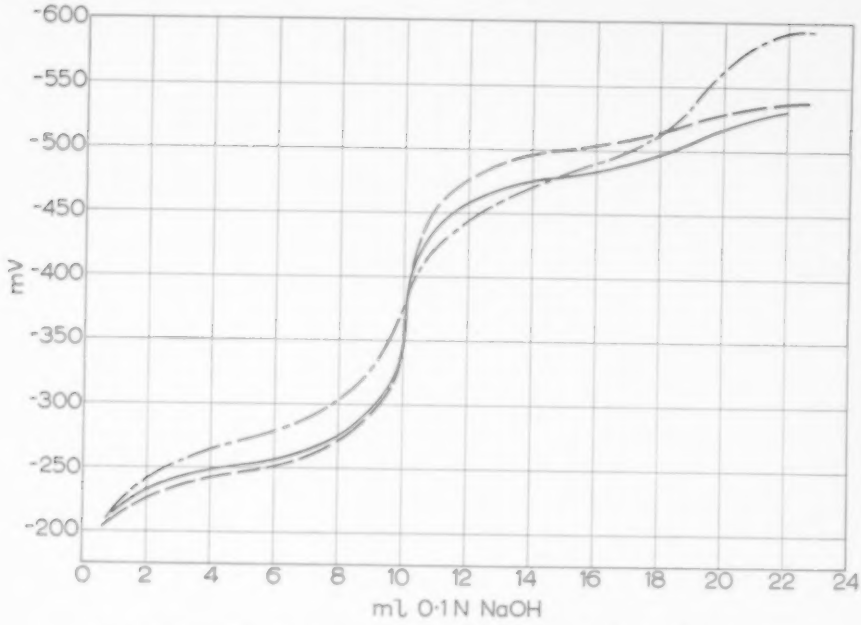


FIG. 1. Titration of 1-(*o*-carboxyphenyl)-pyrazol-3-ones with sodium hydroxide.
VI: ————
VII: — — — —
VIII: —.—.—.

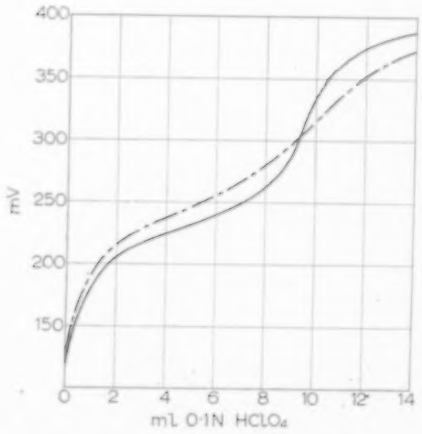


FIG. 2. Titration of 1-(*o*-carboxyphenyl)-pyrazol-3-ones with perchloric acid in glacial acetic acid.
VI and VII: ————
VIII: —.—.—

but their ethyl esters. In methanolic solution the corresponding methyl esters are formed. When the sodium hydroxide added is too strong (N instead of 0·1 N) a mixture of the free acid and the ester is formed. The formation of the ester may be compared with the formation of acid esters by addition of sodium hydroxide to ethanolic solutions of acid anhydrides.[8] We examined the effect of bases other than the hydroxide or alkoxide ion and found that trimethylamine did not catalyse the ester formation and had no effect on the ethanolic solution of I. On the other hand piperidine did catalyse a reaction, but slower than that catalysed by hydroxyl ions, which led to a mixture of ester and piperidide of VI.

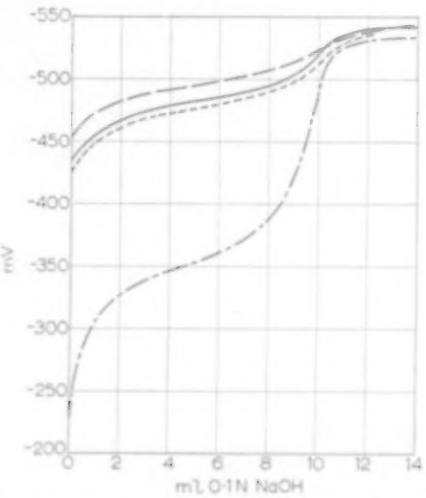


FIG. 3. Titration of 1-(*o*-ethoxycarbonylphenyl)-pyrazol-3-ones and the piperidide of 1-(*o*-carboxyphenyl)-5-methyl-pyrazol-3-one with sodium hydroxide.
Ethyl ester of VI: ———— Ethyl ester of VIII: — · — · — ·
Ethyl ester of VII: — — — — Piperidide of VI: – – – – – –

The esters may be titrated both as acids with sodium hydroxide (ethanolic solution) and as bases with perchloric acid (glacial acetic acid solution). In both instances the absorption of the solution is shifted towards the longer wavelengths during the titration, and most pronounced by titration with sodium hydroxide. Absorption spectra are given below. From Fig. 3 it is seen that the titration curves with sodium hydroxide are typical curves of pyrazol-3-ones, showing no sign of the rather strong acid group which is responsible for the first jump of potential seen on Fig. 1.

From the titration curves with perchloric acid (Fig. 4) it is estimated that pK_B of the three esters are 12·3, 12·4 and 12·4 respectively, i.e. practically the same values as found for the corresponding 1-phenylpyrazol-3-ones and for the open acids. For the methyl ester of VI the pK_B-value is 12·3 as for the ethyl ester.

The piperidide of VI was titrated with sodium hydroxide and with perchloric acid. The pK_B-value was estimated to be 12·4, i.e. neither the carboxyl group nor the ester- or amide-group are modifying the basic properties of the pyrazolone.

[8] S. Veibel and C. Pedersen *Acta Chem. Scand.* **9**, 1674 (1955).

In order to obtain some evidence with regard to structural changes in connection with the opening of one pyrazolone nucleus, with ester formation of the carboxyphenylpyrazolones and with the salt formation of the esters with sodium hydroxide

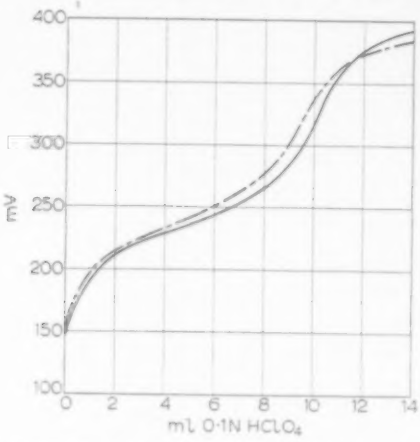


FIG. 4. Titration of 1-(*o*-ethoxycarbonylphenyl)-pyrazol-3-ones with perchloric acid in glacial acetic acid.
Ethyl esters of VI and VII: ———— Ethyl ester of VIII: —·—·—·

or perchloric acid the ultra-violet absorption of these substances was determined. The Figs. 5–10 show that:

(1) The benzo[*c*]pyrazolo[1:2-*a*]pyrazol-1:9-diones have 3 maxima of absorption, at 2000–2300 Å, at 2900 Å and at 3900 Å.

(2) The intensity of absorption in the region 2000–2300 Å is somewhat reduced by the opening of one pyrazolone nucleus, the maximum at 2900 Å is reduced to an inflexion point and the absorption at 3900 Å has been completely abolished.

(3) No significant difference between the absorption spectra of the carboxyphenylpyrazolones and their methyl esters is observed.

(4) The effect of the formation of sodium salts of the methyl esters is the re-establishment of an absorption at 2900–3000 Å which in the sodium salts is broadened towards longer wavelengths, the absorption in the whole region 2900–3900 Å being much more pronounced than for the ester in neutral solution.

(5) Salt formation with perchloric acid does not produce any significant difference in absorption.

EXPERIMENTAL

Preparation of β-acetyl o-carboxyphenylhydrazine, $HOOCC_6H_4NHNHCOCH_3$, *and β,β-diacetyl o-carboxyphenylhydrazine,* $HOOCC_6H_4NHN(COCH_3)_2$

The acetylation of *o*-carboxyphenylhydrazine was carried out according to standard procedures for the acetylation of arylhydrazines. *o*-Carboxyphenylhydrazine was liberated from an aqueous 5 per cent solution of its hydrochloride. The solution can be decolorised by shaking at room temperature with norite or charcoal. It was then filtered, cooled in ice water and cautiously neutralised with a little less than the calculated amount of 10 N sodium hydroxide, added dropwise to the mechanically stirred solution. The precipitate was filtered off and the filtrate tested for complete

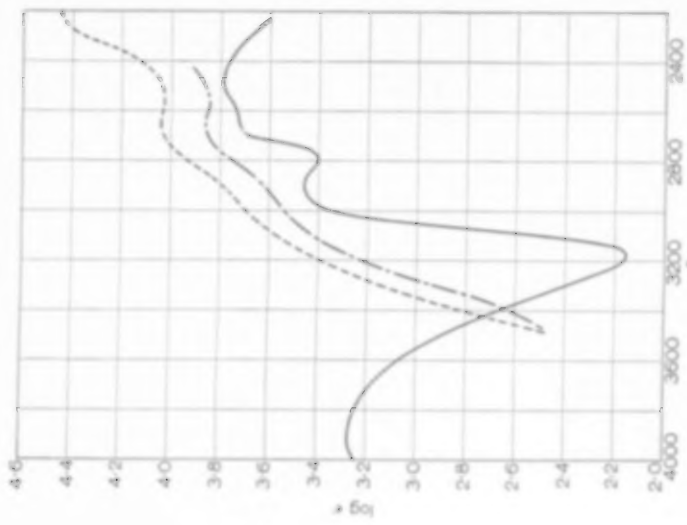


FIG. 6. Absorption of ultra-violet by 2-ethyl-3-methyl-benzo[e]pyrazolo[1,2-a]pyrazol-1:9-dione, 1-(o-carboxyphenyl)-4-ethyl-5-methyl-pyrazol-3-one and 1-(o-ethoxycarbonyl-phenyl)-4-ethyl-5-methylpyrazol-3-one. Solvent: 96 per cent ethanol.
II: ———— VII: — · — · — · Ethyl ester of VII: - - - - -

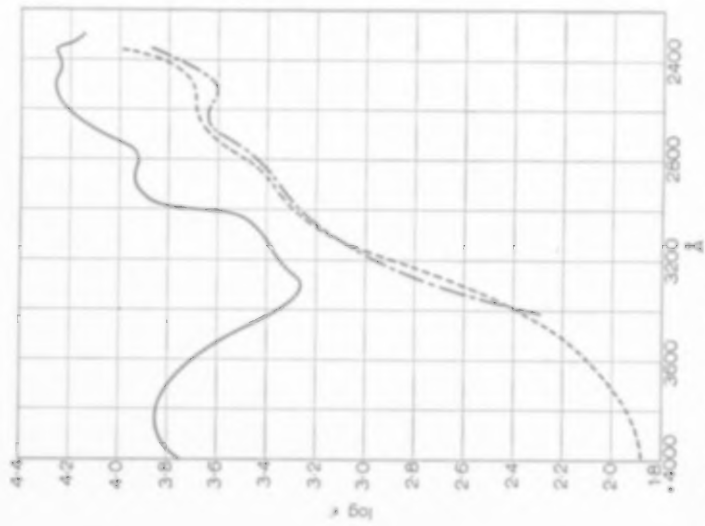


FIG. 5. Absorption of ultra-violet by 3-methyl-benzo[e]pyrazolo[1,2-a]pyrazol-1:9-dione, 1-(o-carboxyphenyl)-5-methyl-pyrazol-3-one and 1-(o-ethoxycarbonylphenyl)-5-methyl-pyrazol-3-one. Solvent: 96 per cent ethanol.
I: ———— VI: — · — · — · Ethyl ester of VI: - - - - -

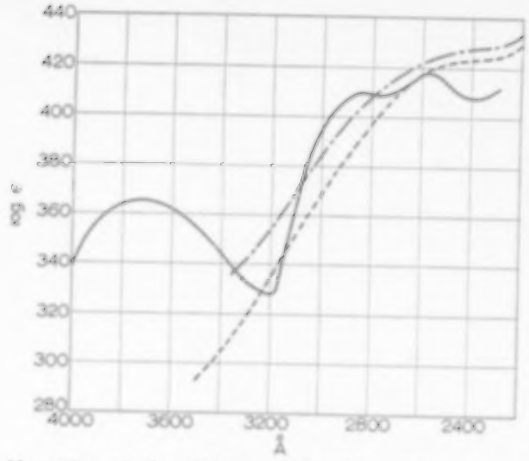


FIG. 7. Absorption of ultra-violet by 3-phenyl-benzo[*c*]pyrazolo[1,2-*a*]pyrazol-1:9-dione, 1-(*o*-carboxyphenyl)-5-phenyl-pyrazol-3-one and 1-(*o*-ethoxycarbonylphenyl)-5-phenyl-pyrazol-3-one. Solvent: 96 per cent ethanol.
III: ———— VIII: — · — · — · Ethyl ester of VIII: – – – – – –

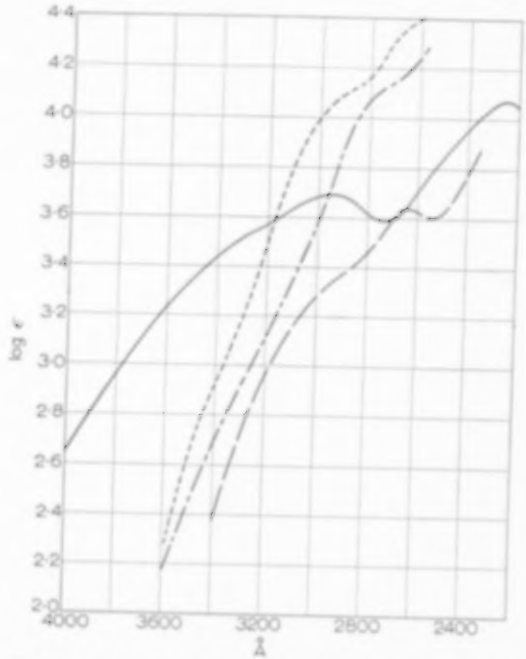


FIG. 8. Absorption of ultra-violet by 1-(*o*-methoxycarbonylphenyl) 5-methyl-pyrazol-3-one and its sodium salt, solvent 96 per cent ethanol, and of its perchlorate, solvent glacial acetic acid.
Methyl ester of VI: — — — —
Sodium salt of the methyl ester: ————
Methyl ester of VI in glacial acetic acid: – – – – – –
Perchlorate of the methyl ester: — · — · — ·

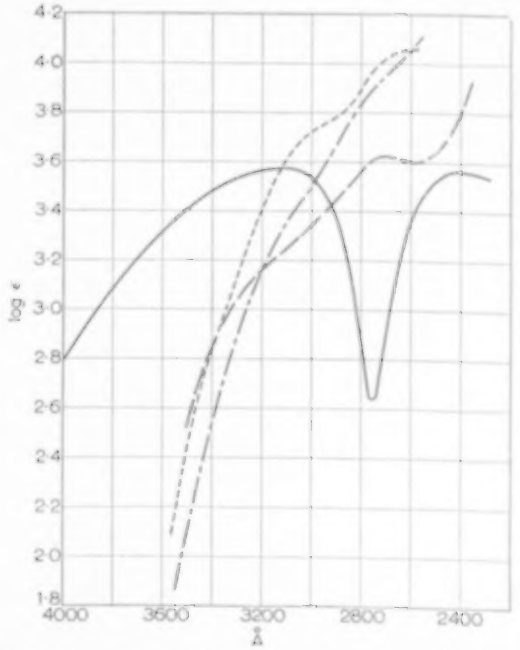


FIG. 9. Absorption of ultra-violet by 1-(*o*-methoxycarbonyl)-4-ethyl-5-methyl pyrazol 3-one and its sodium salt, solvent 96 per cent ethanol, and of its perchlorate, solvent glacial acetic acid.
Methyl ester of VII: — — — —
Sodium salt of the methyl ester: ————
Methyl ester of VII in glacial acetic ester: – – – – –
Perchlorate of the methyl ester: — · — · —

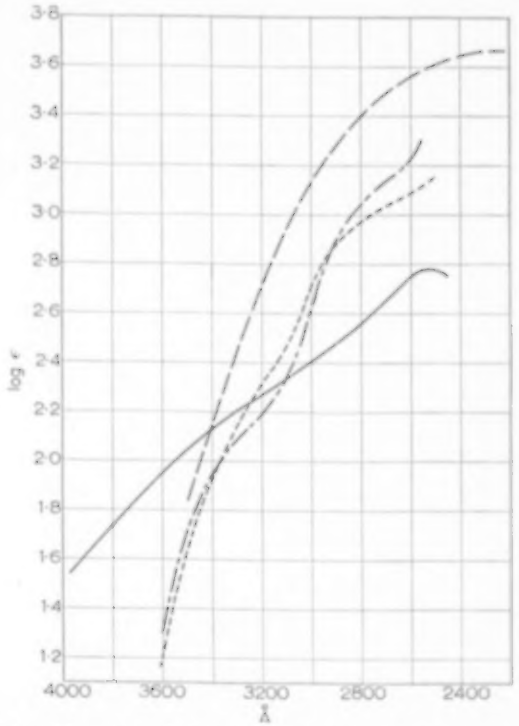


FIG. 10. Absorption of ultra-violet by 1-(*o*-methoxycarbonyl)-5-phenyl-pyrazol-3-one and its sodium salt, solvent 96 per cent ethanol, and of its perchlorate, solvent glacial acetic acid.
Methyl ester of VIII: — — — —
Sodium salt of the methyl ester: ————
Methyl ester of VIII in glacial acetic acid: – – – – –
Perchlorate of the methyl ester: — · — · —

neutralisation by addition of further 1-2 ml of 10 N sodium hydroxide. All precipitates were collected on the same filter, washed with water, ethanol and ether and finally air-dried.

The temperature was kept low at all stages of the reaction in order to avoid formation of benzopyrazolone by ring closure.

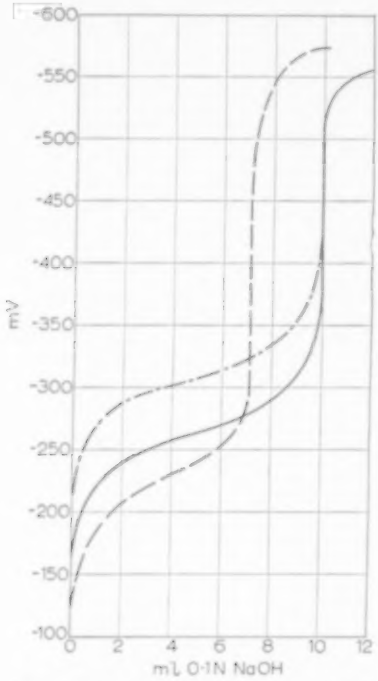


FIG. 11. Titration of β-acetyl *o*-carboxyphenylhydrazine, β,β-diacetyl-*o*-carboxyphenylhydrazine and 1-acetyl benzopyrazol-3-one.
β-Acetyl *o*-carboxyphenylhydrazine: ————
β,β-Diacetyl *o*-carboxyphenylhydrazine: — — — —
1-Acetyl benzopyrazol-3-one: — . — . — .

The free *o*-carboxyphenylhydrazine was refluxed for 2 hr with 8–10 parts (by weight) of glacial acetic acid. A quarter of the solvent was then removed *in vacuo* (bath temperature 50–60°C). The residue was cooled in water and filtered through a sintered-glass filter, washed with water and air-dried. A further crop was gained by diluting the filtrate with 2–3 volumes of water. Total yield was 68 per cent and the m.p. 243–245°C, indicating that the substance during the heating was converted into benzopyrazolone, m.p. 244°C.[9]

We tried to improve the yield by addition of 10 per cent acetic anhydride to the refluxing mixture. The result was, however, that the yield of β-acetyl *o*-carboxyphenylhydrazine was reduced and another substance with m.p. 200°C was formed in a yield of 20–30 per cent. This substance showed by electrometric titration with 0·1 N sodium hydroxide (solvent : ethanol) mol. wt. = 237·9 against 194·2 calculated for β-acetyl *o*-carboxyphenylhydrazine. The two titration curves are shown in Fig. 11. The new substance gave the following results on analysis (Found: C, 55·70; H, 5·00;

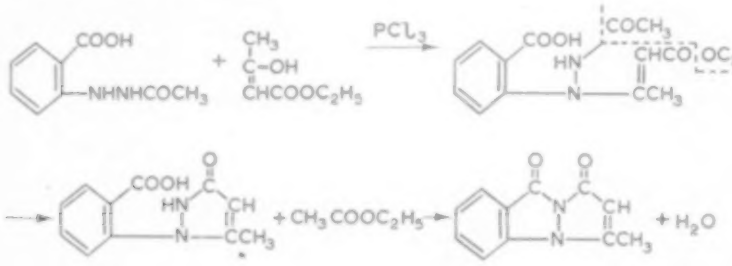
N, 11·92. mol. wt. = 237·9. $C_{11}H_{12}O_4N_2$ requires C, 55·92; H, 5·10; N, 11·86 per cent. mol. wt. = 236·2*).

This corresponds to a diacetyl derivative of *o*-carboxyphenylhydrazine. As the substance is not converted into a benzopyrazolone derivative on heating the structure *β*,*β*-diacetyl *o*-carboxyphenylhydrazine is more probable than the structure *α*,*β*-diacetyl *o*-carboxyphenylhydrazine.

3-*Methyl-benzo*[*c*]*pyrazolo*[1:2-*a*]*pyrazol*-1:9-*dione* (I)

In a 100–150 ml flask connected by a ground-glass joint to a reflux condenser 19·4 g (0·1 mole) of *β*-acetyl *o*-carboxyphenylhydrazine was thoroughly mixed with 26 g (0·2 mole) of ethyl acetoacetate. Eighteen ml (0·2 mole) of phosphorus trichloride were added dropwise through the reflux condenser, starting a reaction accompanied by evolution of hydrogen chloride. The vigorous reaction was controlled by cooling the flask in iced water. When all the phosphorus trichloride had been added the flask was left at room temperature for 2 hr with frequent shaking and then heated for some hours on the steam-bath till the evolution of hydrogen chloride had ceased. It was then left overnight at room temperature, whereupon 50 ml of water were added in small quantities, precipitating yellow crystals which were filtered through a sintered-glass filter and purified by recrystallisation from 10 parts (by weight) of glacial acetic acid or 20 parts (by weight) of 96 per cent ethanol.

The reactions are as follows:



Yield 12–14 g (60–70 per cent) with m.p. 268–270°C, Michaelis[2] gave m.p. 265°C (Found: C, 66·22; H, 3·92; N, 14·05 per cent. Calc. for $C_{11}H_8O_2N_2$: C, 66·00; H, 4·03; N, 14·00 per cent. mol. wt. = 200·2).

A diluted solution of the substance in glacial acetic acid shows a very brilliant blue fluorescence. Ethanolic solutions, too, are fluorescent, but not so brilliantly as are the acetic acid solutions.

2-*Ethyl*-3-*methyl-benzo*[*c*]*pyrazolo*[1:2-*a*]*pyrazol*-1:9-*dione* (II)

In a flask equipped as above 19·4 g (0·1 mole) of *β*-acetyl *o*-carboxyphenylhydrazine were thoroughly mixed with 24 g (0·15 mole) of ethyl *α*-ethylacetoacetate. Eighteen ml (0·2 mole) of phosphorus trichloride were added and the flask was heated slightly in order to start the reaction which was then continued, allowing the flask to stand for 2 hr at room temperature and then for 4 hr on the steam-bath and again at

* All microanalyses were done by Mr. Preben Hansen, Universitetets kemiske Laboratorium.

[2] E. Fischer *Ber. Dtsch. Chem. Ges.* **13**, 680 (1880).

room temperature overnight. The following day the reaction was continued by heating once more on the steam-bath to ascertain that the evolution of hydrogen chloride had ceased. It was then cooled and 50 ml of iced water or, preferably, 100 ml of 96 per cent ethanol were added, hydrolysing the excess of phosphorus trichloride and leaving a resinous precipitate which crystallised when left overnight covered with ethanol. The crystals were isolated by filtration and recrystallised from 20–40 parts (by weight) of 96 per cent ethanol or 10 parts (by weight) of glacial acetic acid. Yield 6–7 g (25–28 per cent), m.p. 185°C (Found: C, 68·36; H, 5·31; N, 12·26. $C_{13}H_{12}O_2N_2$ requires C, 68·41; H, 5·30; N, 12·28 per cent. mol. wt. = 228·2).

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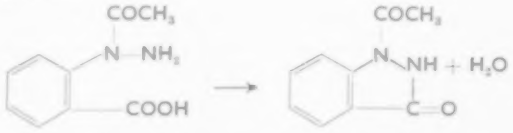
3-Phenyl-benzo[c]pyrazolo[1:2-a]pyrazol-1:9-dione (III)

The preparation of this compound was more difficult than that of the two first mentioned substances. It is recommended not to work with more than 0·05 mole (10 g) of β-acetyl *o*-carboxyphenylhydrazine and 0·075 mole (15 g) of ethyl benzoylacetate in each charge. The components were intimately mixed. Nine ml (0·2 mole) of phosphorus trichloride were added and the mixture was left at room temperature for some hours and then cautiously heated to 50–80°C for several hours. When the evolution of hydrogen chloride had ceased the flask was cooled and 50 ml of 96 per cent ethanol added, keeping the mixture cold by placing the flask in an iced bath. A resinous mass was formed which when left at room temperature covered with ethanol for a couple of days eventually crystallised. The crystals were isolated by filtration and recrystallised from 10–20 parts (by weight) of 96 per cent ethanol. Yield 4–4·5 g (30·35 per cent), m.p. 197–300°C (Found: C, 73·10; H, 3·85; N, 10·52. $C_{16}H_{10}O_2N_2$ requires C, 73·27; H, 3·84; N, 10·68 per cent. mol. wt. = 262·3).

Isolation of 1-acetyl benzopyrazol-3-one

Accompanying the formation of the substituted benzo [*c*] pyrazolo [1:2-*a*] pyrazol-1:9-diones a ring closure of the acetylated *o*-carboxyphenylhydrazine to benzopyrazol-3-one or an acetylated benzopyrazol-3-one may take place. From β-acetyl *o*-carboxyphenyl-hydrazine the unsubstituted benzopyrazol-3-one is easily prepared on heating. It has, as mentioned above, m.p. 244°C. From the reaction mixtures mentioned above we were able sometimes to isolate colourless crystals with m.p. 214–215°C which on analysis showed the composition $C_9H_8O_2N_2$, corresponding to an acetyl derivative of benzopyrazol-3-one (Found: C, 61·10; H, 4·96; N, 16·22. $C_9H_8O_2N_2$ requires C, 61·34; H, 4·57; N, 15·90 per cent. mol. wt. = 176·2).

As this substance can be titrated with sodium hydroxide (Fig. 11) and not with perchloric acid we consider it as 1-acetyl benzopyrazol-3-one, formed from α-acetyl *o*-carboxyphenyl-hydrazine present as an impurity in the preparations of β-acetyl *o*-carboxyphenyl-hydrazine used:



Opening of the ring B by addition of water or sodium hydroxide

Compounds I–III suspended in water and treated with 2 equivalents of sodium hydroxide were converted into the disodium salts of the corresponding substituted

1-*o*-carboxyphenylpyrazol-3-ones VI–VIII. Heating is unnecessary and should be avoided. Upon addition in the cold of 2 equivalents of dilute hydrochloric acid the free acids VI–VIII were precipitated. VI. m.p. 232–234°C, Michaelis[2] gave m.p. 221° (Found: C, 60·25; H, 4·53; N, 12·71. Calc. for $C_{11}H_{10}O_3N_2$: C, 60·51; H, 4·62; N, 12·844 per cent. mol. wt. = 218·2). VII. m.p. 215°C (Found: C, 63·13; H, 5·63; N, 11·55. $C_{13}H_{14}O_3N_2$ requires C, 63·38; H, 5·73; N, 11·38 per cent. mol. wt. = 246·3). VIII. m.p. 273–275°C (Found: C, 68·50; H, 4·46; N, 10·16°C. $C_{16}H_{12}O_3N_2$ requires C, 68·54; H, 4·33; N, 10·00 per cent. mol. wt. = 280·3). As indicated above these acids behave as dibasic acids when titrated in ethanolic solution with 0·1 N sodium hydroxide and as monoacid bases when titrated in glacial acetic acid solution with perchloric acid. Titration curves are seen in Figs. 1–2. Heated above the m.p. the acids lose water with closure of ring B.

Opening of the ring B by addition of sodium methoxide or sodium ethoxide

To a solution or suspension of 0·01 mole of the substances I–III in 200–300 ml of methanol or ethanol (96 per cent or absolute) 100 ml of 0·1 N sodium hydroxide (aqueous, methanolic or ethanolic) were added with mechanical stirring during 1/2–1 hr. The strong fluorescence of the solution vanishes during the addition. The solution was filtered in order to remove any undissolved particles, and the filtrate acidified with 0·01 mole of hydrochloric acid. The neutralised solution was evaporated to dryness *in vacuo* (bath temperature 30–40°C). The residue was extracted with 10–20 ml of hot methanol or ethanol, according to the solvent originally used. On cooling, the filtrate deposits crystals of the methyl- or ethyl ester of VI–VIII. Yield 70–80 per cent.

Methyl ester of VI, m.p. 163–164°C (Found: C, 62·07; H, 5·06; N, 12·09. $C_{12}H_{12}O_3N_2$ requires C, 62·07; H, 5·21; N, 12·07 per cent. (mol. wt. = 232·2).

Ethyl ester of VI, m.p. 160–161°C (Found: C, 63·28; H, 5·50; N, 11·42. $C_{13}H_{14}O_3N_2$ requires C, 63·38; H, 5·73; N, 11·38 per cent. mol. wt. = 246·3).

Methyl ester of VII, m.p. 168–169°C (Found: C, 64·51; H, 6·34; N, 10·52. $C_{14}H_{16}O_3N_2$ requires C, 64·58; H, 6·20; N, 10·76 per cent. mol. wt. = 260·3).

Ethyl ester of VII, m.p. 150–151°C (Found: C, 65·60; H, 6·77; N, 10·21. $C_{15}H_{18}O_3N_2$ requires C, 65·69; H, 6·57; N, 10·22 per cent. mol. wt. = 274·3).

Methyl ester of VIII, m.p. 135–136°C (Found: C, 69·47; H, 4·97; N, 9·49. $C_{17}H_{14}O_3N_2$ requires C, 69·38; H, 4:79; N, 9·52 per cent. mol. wt. = 294·3).

Ethyl ester of VIII, m.p. 129–130°C (Found: C, 70·18; H, 5·00; N, 9·08. $C_{18}H_{16}O_3N_2$ requires C, 70·13; H, 5·23; N, 9·09 per cent. mol. wt. = 308·3).

To catalyse the ring-opening with bases other than the hydroxyl ion or the alkoxide ion we added trimethylamine to a suspension of I in methanol. No effect was observed. Using piperidine instead of trimethylamine the substance dissolved after prolonged stirring of the suspension, and by the usual procedure a mixture of crystals was obtained from which the methyl ester and another substance was isolated. The latter had m.p. 168–169°C and gave, on titration with perchloric acid, the molecular weight 288, calculated for the piperidide of VI 285·3, for the methyl ester 232·2. The yield was, however, poor and further experiments were not made (Found: C, 67·35; H, 6·50; N, 14·88. $C_{16}H_{19}O_2N_3$ requires C, 67·36; H, 6·71; N, 14·73 per cent.

The esters were all titratable with perchloric acid. The titration curves are given in Figs. 3–4. In all titrations exactly 0·1 millimole of the ester was dissolved in 50 ml of

glacial acetic acid and titrated with a 0·1 N solution of perchloric acid in glacial acetic acid.

The piperidide, too, was titratable with perchloric acid as a monoacid base. Hardly any difference between the piperidide and the methyl ester was observed when 0·1 millimole in 50 ml was titrated.

Absorption of ultra-violet by the substances investigated

The absorption of the ultra-violet by ethanolic or glacial acetic acid solutions was determined with a Beckman DU-spectrophotometer by measuring 1:2000 or 1:5000 solutions of the substances against the solvent (ethanol, ethanol with addition of 1 equivalent of sodium hydroxide, glacial acetic acid or glacial acetic acid with addition of 1 equivalent of perchloric acid).

The absorption curves are given in Figs. 5–10.

Financial support from the Carlsberg Foundation is gratefully acknowledged.

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Tetrahedron, 1957, Vol. 1, pp. 214–220. Pergamon Press Ltd., London

CHEMICAL EFFECTS OF STERIC STRAINS—XIII*

KINETICS OF THE REACTION OF SODIUM BOROHYDRIDE WITH CARBONYL GROUPS— A CONVENIENT TOOL FOR INVESTIGATING THE REACTIVITIES OF ALDEHYDES AND KETONES

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Abstract—The reactions of sodium borohydride in *iso*propyl alcohol with acetone, acetophenone, benzophenone and benzaldehyde show simple second order kinetics, first order in the concentration of borohydride, and first order in the carbonyl component. Benzaldehyde reacts far faster than any of the ketones, corresponding to the greater reactivity of aldehydic carbonyl groups toward attack by nucleophilic reagents. The decrease in rate, acetone > acetophenone and benzophenone, is attributed to the resonance and steric contributions of the aromatic rings. The reaction of sodium borohydride with carbonyl compounds promises to provide a valuable tool for investigating the effect of structure on the reactivity of aldehydes and ketones.

NUMEROUS attempts have been made to examine the effects of structure upon the reactivity of aldehydes and ketones by determining the rates of reactions of these compounds with reagents such as hydroxylamine,[1] phenylhydrazine,[2] and semicarbazide.[3] However, the mechanism of these reactions appears to involve a number of stages and it is not always clear that the same step is rate-determining.[4] A reaction with a kinetically simple rate-determining stage should be quite valuable in facilitating the study of structural effects.

The discovery of sodium borohydride[5] made available a convenient reagent which rapidly reduces carbonyl compounds in suitable solvents.[6] It was demonstrated by Garrett and Lyttle that the reduction of 3α-hydroxy-11α-acetoxypregnan-20-one by sodium borohydride was second order.[7] Relatively rough kinetic studies have indicated that this reaction holds promise for the investigation of structural effects.[8,9] Accordingly a detailed study of the kinetics of the reaction of sodium borohydride

* H. C. Brown and G. Ham *J. Amer. Chem. Soc.* **78**, 2735 (1956).

† Post-doctorate research assistant, 1953-1954, on a grant from the Upjohn Company, Kalamazoo, Michigan.

‡ Post-doctorate research assistant, 1954-1956, on Contract DA-33-008-ORD-992 supported by the Office of Ordnance Research, U.S. Army.

[1] E. Barrett and A. Lapworth *J. Chem. Soc.* **93**, 85 (1908).
[2] G. H. Stempel, Jr. and G. S. Schaffel *J. Amer. Chem. Soc.* **66**, 1158 (1944).
[3] J. B. Conant and P. D. Bartlett *Ibid.* **54**, 228 (1932); F. P. Price, Jr. and L. P. Hammett *Ibid.* **63**, 2387 (1941)
[4] L. P. Hammett *Physical Organic Chemistry* p. 331. McGraw-Hill, New York (1940).
[5] H. I. Schlesinger, H. C. Brown, H. R. Hockstra, and L. R. Rapp *J. Amer. Chem. Soc.* **75**, 199 (1953).
[6] S. W. Chaikin, and W. G. Brown *Ibid.* **71**, 122 (1949).
[7] E. R. Garrett and D. A. Lyttle *Ibid.* **75**, 6051 (1953).
[8] E. H. Jensen *A Study on Sodium Borohydride* NYT Nordisk Forlag Arnold Busck, Copenhagen (1954).
[9] H. C. Brown, E. J. Mead, and B. C. Subba Rao *J. Amer. Chem. Soc.* **77**, 6209 (1955).

with acetone, acetophenone, benzophenone and benzaldehyde was undertaken to test this possibility.

Sodium borohydride has been utilized as a reducing agent primarily in water or methanol solution. It reacts with these solvents, complicating the kinetic study.[7,8] However, it is moderately soluble in *iso*propyl alcohol and exhibits no measurable reaction with this solvent over extended periods of time.[9] Accordingly, *iso*propyl alcohol was selected as the reaction medium.

RESULTS

Solutions of acetone in *iso*propyl alcohol were mixed with solutions of sodium borohydride in the same solvent at 0°. At appropriate intervals of time aliquots were removed and titrated for residual borohydride by the potassium iodate method.[10]

Four moles of ketone react for each mole of borohydride.

$$(CH_3)_2CO + NaBH_4 \rightarrow Na[(CH_3)_2CHO]_4B$$

It was shown in each kinetic run that the overall rates could be expressed by the equation

$$\frac{dx}{dt} = k_2 (a - 4x)(b - x)$$

where a is the initial molar concentration of ketone, b is the initial molar concentration of sodium borohydride, and x is the amount of sodium borohydride which has reacted at time t. Plots of the quantity $\frac{2{\cdot}303}{a - 4b} \log \frac{b(a - 4x)}{a(b - x)}$ against the time t gave straight lines which passed through the origin. (Fig. 1.)

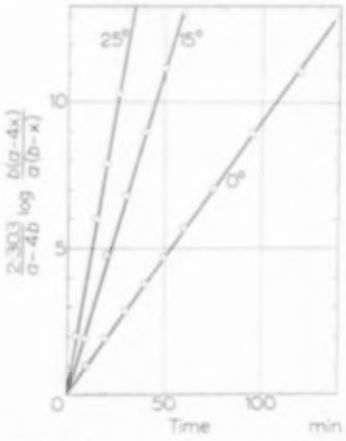


FIG. 1. Second order plots for the reaction of acetone with sodium borohydride in *iso*propyl alcohol at 0°.

The concentration of acetone was varied from 0·0400M to 0·320M and the concentration of borohydride from 0·00970M to 0·0305M without noticeable change in the rate constants, $15{\cdot}1 \times 10^{-4}$ l mole^{-1} sec^{-1}. (This compares with the value 13×10^{-4} l mole^{-1} sec^{-1} observed in a preliminary study of this reaction.[9]) Rate

[10] D. A. Lyttle, E. H. Jensen, and W. A. Struck *Anal. Chem.* **24**, 1843 (1952).

Fig. 2. Temperature dependence of the second order rate constants for the reaction of sodium borohydride with acetone.

Table 1. Second order constants for the reaction of sodium borohydride with carbonyl compounds in *iso*propyl alcohol

Compound	Temp., °C	Initial conc. of compound	Initial conc. of $NaBH_4$	$k_2 \times 10^4$ l. mole^{-1} sec^{-1}
Acetone	0·00 ± 0·01	0·0400	0·0201	15·3
		0·0800	0·0201	15·2
		0·160	0·0204	15·0
		0·320	0·0204	15·0
		0·160	0·0305	15·1
		0·160	0·0159	15·1
			0·00970	15·0
			Mean value	15·1
	15·00 ± 0·02	0·160	0·0175	36·1
	25·00 ± 0·02	0·160	0·0187	63·0
	35·00 ± 0·02	0·160	0·0182	105
Acetophenone	0·00 ± 0·01	0·160	0·0170	2·05
	25·00 ± 0·02	0·0803	0·0182	14·0
		0·161	0·0185	13·7
			Mean value	13·9
	35·15 ± 0·02	0·161	0·0155	26·2
Benzophenone	0·00 ± 0·01	0·0800	0·0213	1·87
	25·00 ± 0·02	0·0400	0·0223	15·8
		0·0800	0·0197	15·9
		0·160	0·0195	15·4
		0·320	0·0172	15·8
		0·160	0·0102	15·9
		0·160	0·0280	15·8
			Mean value	15·8
	35·00 ± 0·02	0·160	0·0193	33·9
Benzaldehyde	−35·3 ± 0·1	0·0416	0·00905	94
	−21·1 ± 0·1	0·0502	0·00848	242
	− 8·7 ± 0·1	0·0390	0·00789	502

constants were also determined at 15·0, 25·0 and 35·0°. The data yielded an excellent log k_2 vs. $1/T$ plot (Fig. 2). The results are summarized in Table 1.

The reactions of sodium borohydride with acetophenone and benzophenone also exhibit second order kinetics, with the rate constants considerably smaller than that observed in the case of acetone. In the case of benzaldehyde the reaction proved to be so fast that it was necessary to utilize both highly dilute solutions and lower temperatures in order to slow the reaction down sufficiently to permit the satisfactory determination of the rate constants.

The results are reported in Table 1.

DISCUSSION

The reaction of acetone with sodium borohydride must involve four successive stages.

$$R_2CO + BH_4^- \xrightarrow{k_2} H_3BOCH(CH_3)_2^-$$

$$R_2CO + H_3BOCH(CH_3)_2^- \xrightarrow{k_2'} H_2B[OCH(CH_3)_2]_2^-$$

$$R_2CO + H_2B[OCH(CH_3)_2]_2^- \xrightarrow{k_2''} HB[OCH(CH_3)_2]_3^-$$

$$R_2CO + HB[OCH(CH_3)_2]_3^- \xrightarrow{k_2'''} B[OCH(CH_3)_2]_4^-$$

In this case, with *iso*propyl alcohol as the solvent, interchange of the alkoxy groups on boron with the solvent should not alter the intermediates involved.[9]

The observed kinetics are consistent with a slow rate-determining reaction for the first stage, with successive stages being considerably faster.[4] This postulate has been confirmed by the preparation of the intermediate, sodium tri-*iso*propoxyborohydride, $NaHB[OCH(CH_3)_2]_3$, and the demonstration that its reaction with acetone is indeed much faster than the reaction of the ketone with sodium borohydride itself.[11]

The observed rate constants may either represent the rate of the direct reaction of borohydride ion with the carbonyl group,

$$\text{C(=O)} + BH_4^- \xrightarrow{k_2} \text{C(OBH}_3^-\text{)—H}$$

or it may represent the product of an equilibrium constant for the association of borohydride ion and the aldehyde or ketone, and the rate constant for the subsequent transfer of a hydride ion to the carbonyl group ($k_2 = Kk$).

$$\text{C(=O)} + BH_4^- \overset{K}{\rightleftharpoons} \text{C(=O)} \cdots H_4B^- \xrightarrow{k} \text{C(OBH}_3^-\text{)—H}$$

A choice between these possibilities does not appear possible at this time. However, irrespective of this difficulty, the structural effects observed with the four carbonyl compounds here examined do appear to be simply related to the structure of the molecules.

[11] H. C. Brown, E. J. Mead, and C. J. Shoaf *J. Amer. Chem. Soc.* **78**, 3613 (1956).

For convenience in following the discussion, the rate constants at 0°, the relative rates and derived data are summarized in Table 2.

TABLE 2. KINETIC DATA FOR THE REACTION OF SODIUM BOROHYDRIDE WITH SELECTED CARBONYL COMPOUNDS IN *iso*PROPYL ALCOHOL

Compound	$k_2 \times 10^5$ (0°) l. mole^{-1} sec^{-1}	Rel. rate (0°)	$E_{act.}$ kcal/mole	log A	$\Delta H^{\ddagger}$ kcal/mole	$\Delta S^{\ddagger}$ e.u.
Acetone	15·1	1·00	9·3	4·59	8·8	−39·1
Acetophenone	2·05	0·136	12·2	6·10	11·7	−32·4
Benzaldehyde	820[a]	53·3	8·0	5·27	7·8	−34·8
Benzophenone	1·87	0·124	13·6	7·18	13·1	−27·7

[a] Calculated from data at lower temperatures.

The decrease in rate from acetone to acetophenone and benzophenone is in accord with the greater steric requirements of the phenyl groups and their ability to conjugate with the carbonyl groups and reduce their sensitivity to attack by nucleophilic reagents.

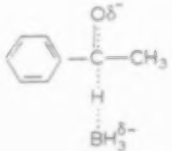
Similarly, the marked difference in the rates for acetophenone and benzaldehyde is in accord with the postulated difference in the inductive and steric effects of the methyl group as compared to the hydrogen atom.

The enthalpy of activation increases by 2·9 kcal/mole from acetone to acetophenone, and increases a further 1·4 kcal/mole to benzophenone. The reactive benzaldehyde molecule exhibits a sharp drop in this quantity.

The entropies of activation are also interesting. The value of −39·1 e.u. for acetone is of the order of magnitude to be expected for a bimolecular reaction. The introduction of a single phenyl group in acetophenone and benzaldehyde results in a somewhat smaller decrease in entropy of activation, while the two phenyl groups in benzophenone result in a further decrease.

These observations can be rationalized in terms of the proposed interpretation of the reaction. In the initial state, resonance interactions between the phenyl group and the carbonyl group should favor a coplanar configuration for the molecule.

On the other hand, in the transition state, the partial transfer of a hydride ion from the borohydride group to the carbon atom of the carbonyl group should reduce the possibilities for such resonance interactions and greatly modify the geometry of the organic moiety



In other words, the restriction to free rotation caused by resonance interactions of one or two phenyl groups with the carbonyl group should largely disappear in the transition state. Thus the difference in entropies of activation for the reactions must largely reflect the differences in the entropies of the carbonyl derivatives.

The simple kinetics and large structural effects observed in this study appear highly promising for the objectives of the present investigation. The results encouraged the application of the reaction to the examination of structural effects in a number of related derivatives with structural features of importance to current theoretical problems. An examination of the reaction of sodium borohydride with cyclic ketones is reported in the following publication.

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EXPERIMENTAL

Materials. Sodium borohydride was carefully purified by recrystallization from diglyme.[9] The product was analysed for active hydrogen by the iodate method, for sodium by titration (as sodium hydroxide) with standard acid and for boron by titration (as boric acid) with sodium hydroxide in the presence of mannitol. The analysis indicated the composition $Na_{1\cdot000}\ B_{1\cdot000}\ H_{4\cdot000}$ with a purity of 99·9 per cent based upon the weight of samples taken.

*Iso*propyl alcohol was dried over Drierite and distilled through a packed column, b.p. 81·6–81·7° at 743 mm, n_D^{20} 1·3772.

Benzophenone was recrystallized from ethanol. It exhibited m.p. 48·1°. The remaining carbonyl derivatives were dried over Drierite and distilled through a packed column. Fractions of constant boiling point and refractive index were utilized. The products exhibited the following properties: acetone, b.p. 55·9–56·0° at 743 mm, n_D^{20} 1·3589; acetophenone, b.p. 82·7–82·8° at 12 mm, n_D^{20} 1·5342; benzaldehyde, b.p. 62·0–62·1° at 10 mm, distilled and handled under nitrogen.

Rate measurements. Standardized solutions of sodium borohydride and of the carbonyl component in *iso*propyl alcohol were prepared. A known volume of the sodium borohydride solution (75 or 100 ml) was placed in a reaction flask with a long narrow neck, immersed in the constant temperature bath. A known volume of the ketone solution, at reaction temperature, was added to the borohydride solution with vigorous mixing. At intervals 10 ml portions of the reaction mixture were withdrawn, added to a large excess of 0·1 N potassium iodate solution (25 or 50 ml) containing 2 g of potassium iodide, followed by 10 ml of 5 N sulfuric acid. The liberated iodine was titrated with 0·1 N sodium thiosulfate.

As previously mentioned, plots of $\frac{2\cdot303}{a-4b}\log\frac{b(a-4x)}{a(b-x)}$ against time gave straight lines passing through the origin for acetone (Fig. 1) and the other ketones. However, in the case of benzaldehyde, the reaction proved to be so fast that this procedure yielded erratic results. The procedure was therefore modified.

A small thin glass bulb containing 5·00 ml of benzaldehyde solution was placed in a large test tube and 10 ml of the sodium borohydride solution was added. The tube was brought to reaction temperature and the reaction initiated by crushing the bulb and vigorously shaking the tube and its contents in the constant temperature bath. After a suitable reaction time (30 sec for the first measurement), potassium iodate-potassium iodide solution, and then sulfuric acid were added directly to the

test tube and the entire solution titrated for iodine as in the usual procedure. Approximately 10 individual measurements were made for each determination of the rate constant. Typical data are shown in Fig. 3.

FIG. 3. Second order plots for the reaction of benzaldehyde with sodium borohydride in *iso*propyl alcohol at −35·3°.

Usually the second order plots passed through the origin (Fig. 1). However, in the case of benzaldehyde and other carbonyl compounds which react very rapidly, small intercepts are observed (Fig. 3). The reaction of sodium borohydride with carbonyl derivatives proceeds considerably faster in water than in *iso*propyl alcohol (observations of Dr. K. Ichikawa). In the analytical procedure the sample is added to potassium iodate-potassium iodide solution and the reaction is halted by adding sulfuric acid. There is a short interval of time, approximately 30 sec, between the mixing of the sample and the iodate solution and the destruction of the borohydride by the iodine liberated by the sulfuric acid. It is believed that the intercept arises from a small amount of reaction between the borohydride and the carbonyl component in this brief interval.

Tetrahedron, 1957, Vol. 1, pp. 221–230. Pergamon Press Ltd., London

CHEMICAL EFFECTS OF STERIC STRAINS—XIV

THE EFFECT OF RING SIZE ON THE RATE OF REACTION OF THE CYCLANONES WITH SODIUM BOROHYDRIDE

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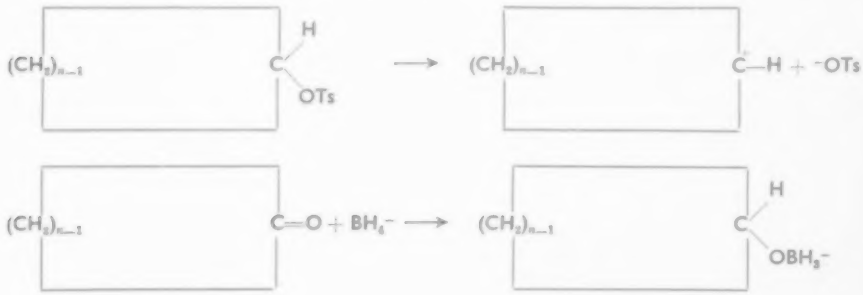
Abstract—The rates of reaction of sodium borohydride with a number of cyclanones (4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 15-, and 17-ring members) were determined at several temperatures in order to ascertain the effect of ring size on the reactivity of the carbonyl group. *Cyclo*butanone is the most reactive of the ketones examined, followed closely by *cyclo*hexanone. *Cyclo*pentanone is considerably less reactive, followed a sharp drop in reactivity in the 7-, 8-, 9-, and 10-ring derivatives. The rate reaches a minimum in the 10-ring and then increases with the larger rings to the value exhibited by the open-chain derivative, di-*n*-hexylketone. The trends in reactivity are very similar to those observed in the equilibrium constants for cyanohydrin formation and in other reactions of ring derivatives. The results agree with the predicted effects of ring size on the magnitude of the internal strains (I-strain).

THE reactivities of ring compounds exhibit a remarkable dependence upon the size of the rings.[1,2] This dependence of the reactivity upon the size of the ring has been attributed to the changes in internal strain accompanying the formation or breaking of a bond to the ring atom in the rate-determining stage.[3–5]

According to this proposal, opposite effects of ring size should be observed in reactions involving the breaking of a bond, such as in the acetolysis of tosylates, and in reactions involving the making of a bond, such as in the reduction of ketones.



Data on the effect of ring size on the rate of solvolysis of cyclanyl tosylates are now available.[6,7] However, rate data for the reactions of ketones are available only for the

* Post-doctorate research assistant, 1954–1956, on Contract DA-33-008-ORD-992, supported by the Office of Ordnance Research, U.S. Army.

[1] V. Prelog *J. Chem. Soc.* 420 (1950).
[2] J. D. Roberts and V. C. Chambers *J. Amer. Chem. Soc.* **73**, 5034 (1951).
[3] H. C. Brown, R. S. Fletcher, and R. B. Johannesen *Ibid.* **73**, 212 (1951).
[4] H. C. Brown and M. Borkowski *Ibid.* **74**, 1894 (1952).
[5] P. D. Bartlett *Bull. Soc. Chim.* C100 (1951).
[6] R. Heck and V. Prelog *Helv. Chim. Acta.* **38**, 1541 (1955).
[7] H. C. Brown and G. Ham *J. Amer. Chem. Soc.* **78**, 2735 (1956).

TABLE 1. RATE CONSTANTS AND DERIVED DATA FOR THE REACTION OF THE CYCLANONES WITH SODIUM BOROHYDRIDE IN ISOPROPYL ALCOHOL SOLUTION

$(CH_2)_{n-1}$ C=O	Temp. (°C)	Rate constant $k_2 \times 10^5$ (l. mole^{-1} sec^{-1})	$E_{act.}$ (kcal mole^{-1})	log A	$\Delta H^{\ddagger}$ (kcal mole^{-1})	$\Delta S^{\ddagger}$ (e.u.)
4	−24·1	56·9	8·6	5·4	8·1	−36·4
	−14·5	115				
	0·1	266				
5	0·0	7·01	9·8	4·7	9·3	−38·8
	25·0	31·8				
	35·1	54·1				
6	−23·7	61·7	5·8	2·9	5·1	−48·1
	−9·2	115				
	0·0	161				
7	0·0	1·02	10·2	4·1	9·6	−41·6
	25·0	4·90				
	35·1	8·54				
8	0·0	0·0781	11·9	4·4	11·3	−41·2
	25·0	0·411				
	35·1	0·963				
9	25·0	0·203	12·2	4·3	11·6	−41·4
	35·1	0·381				
	45·0	0·732				
10	25·0	0·103	13·1	4·6	12·6	−43·5
	35·1	0·218				
	45·0	0·416				
11	25·0	0·152	12·0	4·0	11·4	−42·4
	35·1	0·290				
	45·1	0·537				
12	25·0	1·05	11·3	4·3	10·7	−41·0
	35·1	1·98				
	45·1	3·42				
13	0·0	0·194	11·8	4·7	11·1	−39·2
	25·0	1·22				
	35·0	2·22				
15	0·0	0·420	11·5	4·9	10·8	−38·9
	25·0	2·41				
	35·1	4·61				
17	0·0	0·583	10·7	4·4	10·2	−40·5
	25·0	3·07				
	35·0	5·56				
Di-*n*-hexyl ketone						
	25·0	2·67	11·5	4·9	10·8	−38·8
	35·1	5·05				
	45·0	9·00				

5- and 6-membered rings.[8] The reaction of sodium borohydride with aldehydes and ketones is a kinetically simple reaction which promises to be of considerable utility in examining the reactivity of these compounds.[9] It appeared desirable therefore, to undertake a detailed study of the rates of reaction of sodium borohydride with a wide range of cyclic ketones.

RESULTS

The cyclanones (4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 15- and 17-ring members) were either commercially available products or were synthesized by recognized literature procedures. In each case the compounds were carefully purified prior to use. The rates of reaction were run in *iso*propyl alcohol solution by the procedure previously described.[9]

For comparison of the rates observed for the large rings with those anticipated for related open-chain structures, di-*n*-hexyl ketone was included in the study.

The results are summarized in Table 1.

DISCUSSION

To facilitate ready comparison, the rate constants at 0° for the borohydride reduction reaction are listed in Table 2. Previously available data for the solvolysis of the 1-chloro-1-methyl*cyclo*alkanes,[4] the cyclanyl tosylates,[6,7] and the dissociation of the cyclic cyanohydrins[10] are also included.

TABLE 2. EFFECT OF RING SIZE ON RATE AND EQUILIBRIUM CONSTANTS OF CYCLIC DERIVATIVES

$(CH_2)_{n-1}$ C	Borohydride[a] reduction $k_2 \times 10^4$ (l. mole^{-1} sec^{-1})	Cyanohydrin[b] dissociation, 22–23° (keq., mole l.$^{-1}$)	Solvolysis[c] of tosylates, 70° ($k_1 \times 10^5$ sec^{-1})	Solvolysis[d] of 1-chloro-1-methyl-*cyclo*alkanes, 25° ($k_1 \times 10^2$ hr^{-1})
n				
4	264		26·7	0·224
5	7·01	0·021	32·2	132
6	161	0·001	2·37	1·06
7	1·02	0·13	60·0	115
8	0·0781	0·86	452	303
9	0·0316[e]	1·70	408	46·5
10	0·0132[e]		891[e]	18·8
11	0·0235[e]	1·12	116	12·7
12	0·182[e]	0·31	7·70	
13	0·194	0·26	8·30	3·02
14		0·06	3·12	
15	0·420	0·11	5·18	1·92
16		0·09		
17	0·593	0·12	5·15	2·01
R_2CO	0·454[e,f]		3·15[h]	4·80[i]

[a] This study. [b] Dissociation of cyanohydrin in 96 per cent ethanol (ref. 11). [c] Acetolysis of cyclanyl tosylates (ref. 7, 8). [d] Solvolysis in 80 per cent aqueous ethanol (ref. 5). [e] Calculated from data at other temperatures. [f] Di-*n*-hexylketone. [g] Di-*n*-octylketone. [h] Di-*n*-propylcarbinyl tosylate. [i] Di-*n*-amylmethylcarbinyl chloride.

[8] F. P. Price, Jr. and L. P. Hammett *Ibid.* **63**, 2387 (1941).
[9] H. C. Brown, O. H. Wheeler, and K. Ichikawa *Tetrahedron* **1**, 214 (1957).
[10] V. Prelog and M. Kobelt *Helv. Chim. Acta* **32**, 1187 (1949).

It was previously suggested that the normal bond angle for a carbon atom with co-ordination number 3, as in carbonyl derivatives (> C—O) and carbonium ions (> C^+—H), would be expected to be 120°, as compared to the 109·5° for the normal tetrahedral value. Consequently, the deformation of the angle at the carbonyl carbon atom (120° → ~90°) must be greater than the corresponding deformation for a tetrahedral carbon atom (109·5° → ~90°). It is reasonable to expect that the larger angular deformation will result in a greater strain. Conversion of the carbonyl carbon to a tetrahedral derivative should relieve this additional strain. On this basis it was predicted that reactions of *cyclo*butanone in which the carbonyl carbon atom undergoes transformation from co-ordination number 3 to 4 in the rate-determining step should be strongly favored.[3] In this discussion it is tacitly assumed that the bond oppositions in the *cyclo*butane system are relatively small and may be ignored in view of the large change in angular strain accompanying the change in the configuration of the ring atom.

The rate constant for the reaction of *cyclo*butanone with sodium borohydride is far larger than that for an open-chain compound, such as acetone, and indeed is larger than that of any other ring compound here examined. This result supports the proposed role of angular strain in controlling the reactivity of 3- and 4-membered ring derivatives.[3]

If the change from co-ordination number 3 to co-ordination number 4 is favored in 4-ring systems, the reverse change should be resisted. This prediction is supported by the low rate of solvolysis of 1-chloro-1-methyl*cyclo*butane.[4] It has been pointed out that the solvolysis of *cyclo*butyl tosylate is far greater than would be anticipated on the basis of the considerations here discussed.[2] However, this compound solvolyzes with rearrangement, and it is probable that the solvolysis proceeds directly to the formation of a carbonium ion more stable than the cyclobutyl cation. The theory cannot be applied to such a case; it should be restricted to cases where the rate-determining stage depends primarily upon a simple change in the number of bonds formed by the ring atom undergoing reaction.

In the 5- and 7-ring compounds the bond angles are presumably near the tetrahedral values and angle strain is not believed to be a major factor. The strains in *cyclo*pentane and *cyclo*heptane, which are indicated by heats of combustion studies,[11] are believed to arise from bond opposition forces. On this basis, a change in co-ordination number from 4 to 3 should reduce the number of bond oppositions and the resulting strain in 5- and 7-ring systems. Such reactions should be favored in these ring systems. Conversely, *cyclo*pentanone and *cyclo*heptanone should resist reactions in which the carbonyl carbon is converted into a tetrahedral derivative in the rate-determining stage.

On the other hand, in *cyclo*hexane all of the carbon-to-hydrogen bonds are nicely staggered and there are no bond opposition effects, whereas in *cyclo*hexanone both the angle is unfavorable and two of the *alpha* carbon-to-hydrogen bonds are in partial opposition to the carbon-to-oxygen bond. These considerations lead to the conclusion that changes in co-ordination number from 4 to 3 should be favored in the 5- and 7-ring and resisted in the 6-ring systems, whereas the converse should be true for reactions involving changes in co-ordination number from 3 to 4. In confirmation of

[11] K. S. Pitzer *Science* **101**, 672 (1945); J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer *J. Amer. Chem. Soc.* **69**, 2483 (1947).

this conclusion, the reduction of *cyclo*hexanone is faster than that of any ring ketone other than *cyclo*butanone, with the rate for *cyclo*pentanone and *cyclo*heptanone being much smaller (Table 2).

The available evidence indicates that the medium rings (8- to 12-members) are highly strained,[1] with the strain reaching a maximum in the 10-ring compounds. These strains are believed to arise from both bond opposition forces and compressions of van der Waals radii. Consequently, these ring systems should favor reactions in which bonds to a ring atom are broken and resist reactions in which additional bonds are made. The low rate of reaction with borohydride ion, with a minimum in rate at *cyclo*decanone, is in agreement with this interpretation.

The large rings exhibit reactivities which are considerably lower than that of acetone (k_2 at 0° is 15·1 × 10^{-4} l. mol.$^{-1}$ sec^{-1}), but which are comparable to the higher aliphatic ketones, such as di-*n*-hexyl ketone.

In general, the enthalpies of activation parallel the rate constants. Only in the case of *cyclo*hexanone and *cyclo*butanone do the entropies of activation exhibit a wide variation from the average value of approximately −40 e.u. The higher value for *cyclo*butanone, −36·4, can be accounted for in terms of the relatively high rigidity and order of this ring system.[9] On this basis, the lower value for *cyclo*hexanone might be attributed to a low degree of order in the parent ketone, or to a highly ordered structure in the transition state, or both.

The close similarity in the effects of ring size in the various reactions is indicated in Figs. 1–4. In order to facilitate comparison, the ordinates have been fixed so as to place the points for the 4- and 6-ring systems (either the most reactive, or the least reactive compounds) at the bottom of the diagrams. The remarkable similarity in the effects of ring size on chemical behavior argues for a common factor. This common factor is believed to be the change in internal strain accompanying the change in the co-ordination number of the ring atom undergoing reaction.

The internal strain is made up of several types of interactions: (1) compression of van der Waals radii, (2) the distortion of bond angles, and (3) bond opposition forces.[7] Reactions which proceed with a net decrease in internal strain in the transition state should be favored; those which proceed with a net increase in such strain will be hindered. Ideally, the effect of making or breaking a bond to one of the ring atoms should be analyzed in terms of each of the above strain factors. In actual fact, such an analysis is not possible at the present time. The individual strains are not mutually independent, nor can they be estimated separately with any accuracy at the present time.

On the other hand, the net change in internal strain accompanying the making or breaking of a bond to a ring atom can be estimated with considerable precision. Consequently, it appears desirable to discuss the effect of ring size on chemical behavior in terms of the net change in internal strain accompanying the reaction (I-strain).

It should be recognized that I-strain effects will not be the only factor influencing chemical behavior of ring compounds. It is only claimed that it is an important factor, and in the simple systems here examined it appears to be a dominant factor.

In three of the four reactions considered in Table 2, the maximum or the minimum in the behavior of the system appears at the 10-ring derivative. This behavior is in accord with the evidence that the internal strain is a maximum in the 10-ring compounds.

It is of interest to explore the exception, the solvolysis of the 1-chloro-1-methylcyclanes, where the maximum in rate appears at the 8-ring compound.

Examination of molecular models of the medium rings suggest that compression of van der Waals radii may be involved in the internal strain as well as the bond opposition

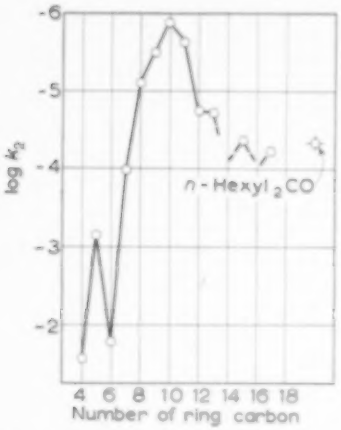


FIG. 1. Effect of ring size on the rate of reaction of sodium borohydride with the cyclanones in isopropyl alcohol at 0°.

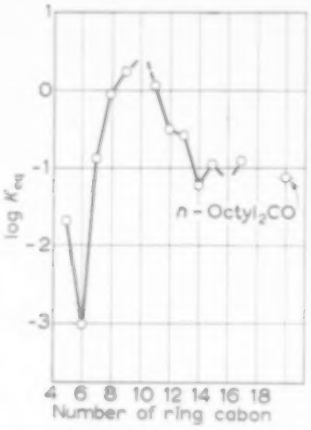


FIG. 2. Effect of ring size on the equilibrium constant for the dissociation of the cyclic cyanohydrins in 96 per cent ethanol at 22–23°.

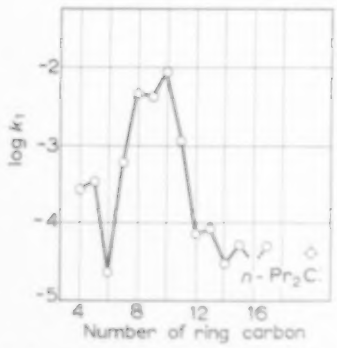


FIG. 3. Effect of ring size on the acetolysis of the cyclanyl tosylates at 70°.

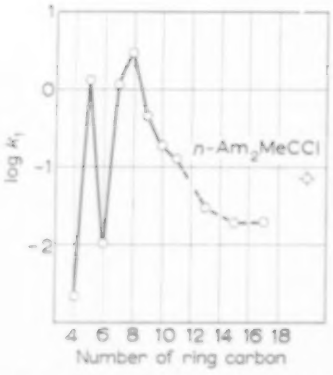


FIG. 4. Effect of ring size on the solvolysis of the 1-chloro-1-methyl-cyclanes in 80 per cent aqueous ethanol at 25°.

forces. On this basis, the introduction of both a methyl group and a chlorine atom on the same carbon atom of a given cyclane molecule may be expected to alter both the internal compressions and the bond opposition forces. There is no reason to expect that both these forces will be equally affected, and the relative magnitude of each effect may vary considerably with the size of the ring and the steric requirements of the substituents.

It would appear that the larger the ring the greater should be its possibilities for modifying its conformation and minimizing the magnitude of the atomic compressions. The maximum observed in the solvolysis of 1-chloro-1-methyl*cyclo*-octane may therefore be attributed to relatively large strains arising from the conflicting steric requirements of the two substituents and the ring hydrogen atoms, superimposed upon the usual bond opposition forces. These atomic compressions are presumably also present in the 10- and 9-ring derivatives, but are reduced to a greater extent than in the smaller ring by modification of the conformation. Conceivably, the maximum in rate could be shifted down as far as the 7-ring, or even further, by a suitable increase of the steric requirements of the substituents.

In general, linear free-energy relationships, such as those pointed out by Hammett for *meta* and *para* aromatic derivatives,[12] are rarely encountered in other than the rigid aromatic systems. The similarity in the structural effects in these ring compounds (Figs. 1–4), encourages an examination of the data from this point of view.

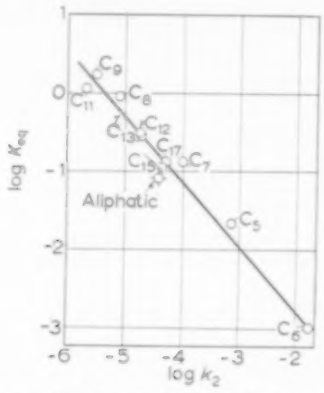
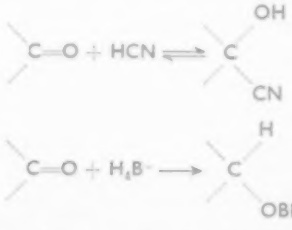


FIG. 5. Free-energy relationship between the equilibrium constants for the dissociation of the cyclic cyanohydrins and the rate constants for the reaction of the cyclanones with sodium borohydride.

Comparison of the equilibrium data for the dissociation of the cyanohydrins with the rate data for the borohydride reaction reveals a reasonably good linear relationship (Fig. 5). The fit is unexpectedly good for systems of this kind and presumably should be attributed to the similarity in the two reactions under comparison.



Comparison of the rate data for the acetolysis of the cyclic tosylates with the rate data for the borohydride reaction also reveals a rough linear relationship for the 5- to 10-ring derivatives (Fig. 6). Larger rings deviate from this relationship and so do

[12] L. P. Hammett *Physical Organic Chemistry* McGraw-Hill, New York (1940).

related aliphatic compounds. The two reactions under comparison must have significantly different steric requirements, so that the deviations are not unexpected.

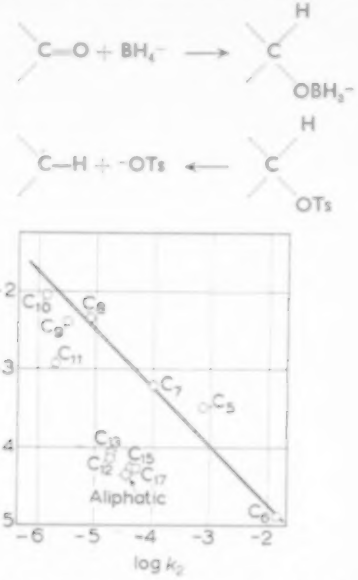


FIG. 6. Free-energy relationship between the rate constants for the acetolysis of the cyclic tosylates and the rate constants for the reaction of the cyclanones with sodium borohydride.

It is the existence of a limited linear relationship for the six consecutive ring systems, 5- through 10-, which must be considered unexpected. The fit, rough as it is, appears to be too good to be considered purely fortuitous. It may be that the fit arises from the fact that the rings from 5- through 10-members are relatively rigid, with comparatively fixed conformations, resembling the aromatic structures in that characteristic, whereas the larger rings possess greater mobility of conformation and more closely resemble aliphatic derivatives.

Carrying the comparison further to the tertiary chlorides, we observe that no linear relationship is indicated (Fig. 7). Presumably this is the result of the much larger steric requirements of the methyl and chlorine substituents in the smaller rings, giving rise to larger strains and enhanced solvolysis rates

As was pointed out, these effects should be less in the larger rings. Presumably these steric interactions result in the points for the 5-, 6-, 7-, and 8-rings being considerably higher than they would otherwise appear in the plot and thereby destroy the linear relationship which might exist in the absence of this effect.

The existence of a limited linear relationship for the solvolysis of the cyclic tosylates and the reaction of the cyclanones with borohydride may have important consequences. A number of strained substances are known which exhibit enhanced rates of solvolysis. In some cases the enhanced rates have been attributed to relief of steric strain.[13] In others, the enhanced rates have been attributed to the formation of unusually stable "non-classical" ions.[14] A rigorous test of the relative importance of these factors in

[13] H. C. Brown *J. Chem. Soc.* 1248 (1956).
[14] S. Winstein *Bull. Soc. Chim.* **18**, 55 (1951).

various systems has been rendered difficult by the transient nature of these carbonium ions.

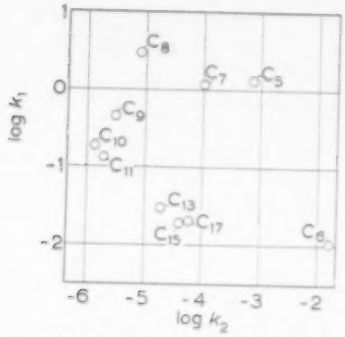


FIG. 7. Free-energy relationship between the rate constants for the solvolysis of the 1-chloro-1-methyl*cyclo*alkanes and the rate constants for the reaction of the cyclanones with sodium borohydride.

Conceivably, the carbonyl derivatives may provide relatively stable models of carbonium ions of related structures.

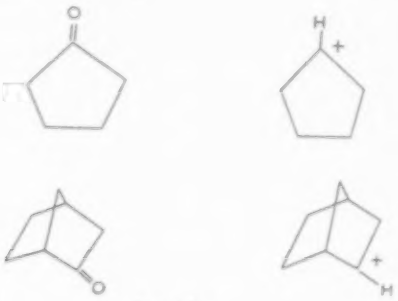
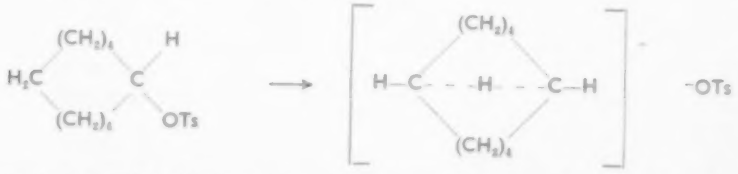


FIG. 23a.

For example, we have attributed the high rate of solvolysis of *cyclo*decyl tosylate to relief of internal strain accompanying the ionization. On the other hand, the alternative possibility that the high rate is due to the formation of a relatively stable "non-classical" *cyclo*decyl cation has been considered.[6]



Such a structure would, of course, provide a reasonable explanation for the facile transannular hydride shifts which are observed in this ring system.[15]

However, from Fig. 6 it appears that the high rate of solvolysis of *cyclo*decyl tosylate is not out of line with the low reactivity of *cyclo*decanone. Since "non-classical" structures for this cyclic ketone are of questionable importance, it does not

[15] V. Prelog and K. Schenker *Helv. Chim. Acta* **35**, 2044 (19).52
V. Prelog, K. Schenker, and W. Kung *Ibid.* **36**, 471 (1953).

appear desirable in the absence of additional evidence to attribute the high reactivity of *cyclo*decyl tosylate to this type of stabilization of the *cyclo*decyl cation.

We are presently investigating this experimental approach, utilizing the carbonyl compounds as models for related carbonium ions, in the hope of attaining a more complete understanding of the factors influencing the rates of formation and the stability of carbonium ions.

EXPERIMENTAL PART

Materials. The purifications of *iso*propyl alcohol and sodium borohydride have been described previously.[9] The carbonyl compounds were either commercial samples, carefully purified, or were synthesized by standard procedures. The physical properties of the cyclic ketones used in the rate measurements are summarized in Table 3.

TABLE 3. PHYSICAL PROPERTIES OF CYCLANONES

$(CH_2)_{n-1}C{=}O$	B.p. (°C/mm)		M.p. (°C)		n_D^{20}	
	Obsd.	Lit.	Obsd.	Lit.	Obsd.	Lit.
n						
4	98·2/743	98–100/760[a]			1·4209	1·4189(25°)[a]
5	130·5/744	129·5/761[b]			1·4363	1·4370–1·4373[c]
6	153·8/744	155·7/760[d]			1·4502	1·45066(19·3°)[d]
7	180·0/744	66–70/16[e]			1·4610	1·4608[e]
8			43·5	43·8[e]		
9	97·5/15	92–95/12[b]			1·4475	1·4730(17°)[f]
10			24·5–25	20–22[g]		
11	106/10	108/10[f]			1·4810	1·4786(17°)[f]
12			61–62	60–61[h]		
13			29·5–30·5	30–32[h]		
15			63	63[f]		
17			65	63[f]		

[a] J. D. Roberts and C. W. Sauer *J. Amer. Chem. Soc.* **71,** 3925 (1949). [b] I. Vogel *J. Chem. Soc.* 2030 (1928). [c] E. R. Johnson and W. D. Walters *J. Amer. Chem. Soc.* **76,** 6266 (1954). [d] J. Timmermans and H. Roland *J. Chem. Phys.* **34,** 693 (1937). [e] W. Herz and W. Bloch *Z. physik. Chem.* **104,** 433 (1923). [f] R. H. Cox *J. Amer. Chem. Soc.* **74,** 2924 (1952). [g] E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson *Ibid.* **61,** 1057 (1939). [h] V. Prelog, L. Frenkiel, M. Kobelt, and P. Barman *Helv. Chim. Acta* **30,** 1741 (1947). [i] L. Ruzicka and W. Brugger *Ibid.* **9,** 399 (1928). [j] L. Ruzicka, M. Stoll, and H. Schinz *Ibid.* **9,** 249 (1928). [k] L. Ruzicka, M. Stoll, H. W. Huyser, and H. A. Bockenoogen *Ibid.* **13,** 1152 (1930).

Kinetic measurements. The experimental procedure was identical with that reported previously.[9] The temperatures were controlled to less than ±0·02° except for temperatures below 0°, where the variation was of the order of ±0·1°. Several individual determinations, with varying initial concentrations of reactants, were carried out for a number of the compounds. In these cases the individual rate constants usually agreed to within 1 per cent. The quality of the agreement realized was similar to that reported in Table 1.[9] Where multiple determinations were available, the mean values of the second-order rate constants are reported in Table 1. For the less accessible ring derivatives, the value of the material made it advisable to restrict our measurements to a single kinetic run at each temperature.

Tetrahedron, 1957, Vol. 1, pp. 231–237. Pergamon Press Ltd., London

HIGH PURITY PREPARATION OF THE BENZENE CARBOXYLIC ACIDS GIVING SOLID, NEUTRAL METHYL ESTERS*

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(*Received* 25 *April* 1957)

Abstract—The preparation and purification of the nine benzene carboxylic acids giving solid, neutral methyl esters and of these esters are described. By acid hydrolysis of these esters the corresponding benzene carboxylic acids are prepared in a high state of purity and in quantitative yields. The purities of the acids which have no definite melting-points were checked by reference to the material balances of the hydrolyses of the esters in conjunction with the elementary analyses of the acids. Corrected melting-points are given for the esters. Data in the literature are also examined and criticised in the light of the present results.

INTRODUCTION

BENZENE carboxylic acids appear frequently in structural studies as degradation products from the oxidation of many aromatic substances, both natural and synthetic. It is well known, for example, that oxidation of coals, lignins, rosin, and similar materials results in the production of mixtures of these acids.[1,2] Although the structures of these acids were definitely established at an early date, there has been some confusion between those of the 1-2-3-4-and 1-2-3-5-isomers. Baeyer, who discovered these two acids,[3] named them "mellophanic acid" for the 1-2-3-4-isomer and "prehnitic acid" for the 1-2-3-5-compound. Due to the fact that the accepted name for the 1-2-3-4 tetramethylbenzene is "prehnitene" this nomenclature was unfortunate and was the origin of several contradictory investigations for establishing the true structures of these two acids. Bamford and Simonsen,[4] Freund and Fleischer,[5] and more recently Smith and co-workers[6,7] conclusively established the constitution of both acids, confirming Baeyer's structures and refuting the objections of Jacobsen.[8] Smith and Birkyt[6] proposed reversing the original assignments in order to use the name "prehnitic" for the acid derived from "prehnitene" (1-2-3-4-tetramethylbenzene). Roy and Howard[9] have supported this proposal which is also favoured here. Read and Purves[10] have suggested discontinuing the use of both trivial names.

In spite of the laboratory importance of these acids in structural studies and of the commercial importance of some of them, particularly the lower members, very

* Presented at the XIV International Congress of Pure and Applied Chemistry (Organic Chemistry), Zurich, July 21–27 1955.

[1] H. C. Howard *Chemistry of Coal Utilization* (H. H. Lowry, editor), Chapter 18. John Wiley & Sons, Inc., New York (1945).
[2] F. González-Sánchez *Combustibles* (*Zaragoza*) **14**, 3 (1954).
[3] A. v. Baeyer *Ann.* **141**, 271 (1867); *Ibid.* **7**, suppl., 1 (1870).
[4] H. Bamford and J. L. Simonsen *J. Chem. Soc.* **97**, 1904 (1910).
[5] M. Freund and K. Fleischer *Ann.* **411**, 14 (1916).
[6] L. I. Smith and G. D. Byrkit *J. Amer. Chem. Soc.* **55**, 4305 (1933).
[7] L. I. Smith and E. J. Carlson *J. Amer. Chem. Soc.* **61**, 288 (1939).
[8] O. Jacobsen *Ber. Dtsch. Chem. Ges.* **17**, 2516 (1884).
[9] A. N. Roy and H. C. Howard *J. Amer. Chem. Soc.* **74**, 3239 (1952).
[10] D. E. Read and C. B. Purves *J. Amer. Chem. Soc.* **74**, 116 (1952).

little is known about the properties of this series of acids as a whole. This lack of data on the benzene carboxylic acids became apparent to the author during the course of an investigation dealing with the study of the acid mixtures obtained by oxidation of coal.[11] While there are already methods for the preparation of these acids in a crude condition, no systematic work describing their preparation and purification to a high degree of purity can be found, except in connection with the lowest members. This may be due partly to the fact that with the exclusion of the benzoic acid, the remaining eleven benzene carboxylic acids have no true melting points. The acids form anhydrides, and decompose or sublime near or at the melting temperatures. Reported m.p.s. vary therefore widely as shown in Table 1, which is a representative compilation of recorded m.p.s of these acids and their neutral, methyl esters. Because of this, it is impossible to follow by the rise in m.p. the purification of these acids by crystallisation. The neutral, methyl esters of benzoic, *o*-phthalic and trimellitic (1-2-4) acids are liquid. The remaining nine esters of the benzene carboxylic acids are solid. Small variations are found in the m.p.s reported by different authors (Table 1).

Under these circumstances, it did appear convenient to undertake a study to develop methods of preparation and purification of the benzene carboxylic acids and

TABLE 1. M.P. OF THE BENZENE CARBOXYLIC ACIDS AND THEIR NEUTRAL, METHYL ESTERS

	Acid, m.p., °C	Ester, m.p., °C
Benzoic	122·43[a]; 122·305[b]; 122·375[c]; 122·45[d]	Liq.
Phthalic (1–2)[e]	Subl. 200–208[a]	Liq.
Isophthalic (1–3)	Subl. without melting, 348·7[b]	67–68[d]; 68[a]; 64–65[d]; 66–67[c]; 71[d]
Terephthalic (1–4)	Subl. without melting	140[a]; 140–141[d]; 141–142[c]; 140[d]; 140·8[c]; 140·5–141[d]
Hemimellitic (1-2-3)	190 dec.[b,c]; 197[a]; 190[b]	100[c,d]; 101–102[d]
Trimellitic (1-2-4)[f]	216–219[g]; 221[a,b]; 215–217 o.c., 229–234 c.c.[b]; 235[c]; 228[b,c,d]; 228 dec.[c,d,b]; 215[g]; 220–235[a]; 210[a]; 217–220[d]	Liq.
Trimesic (1-3-5)	345–350[a]; 375–380[b]; 380[d]; 360[b,d]; 379[d]	143[a]; 143–144[a,b,d,g]; 142[b,d]
Prehnitic (1-2-3-4)	215 soft.–238[g]; 241 dec.[d]; 238 dec.[b]; 238–242 dec. o.c., 264–267 dec. c.c.[g]; 236–238[a]; 241–244[d]	133–135[d]; 129[a,b]; 129–130[d]; 130–131[b,d]; 131–133[a]; 132[g]
Mellophanic (1-2-3-5)	240 soft.[b,d,g,h,d]; 250[g]; 253–262[d]; 252[d]; 238–253[a]; 263–266[b]; 243–247[d]	108–109[d]; 107–109[g]; 110–111[d]; 111–116[d]
Pyromellitic (1-2-4-5)	264[g]; 265–268[a,b]; 273–275[c]; 275[d]; 260 soft.–279[g]; 270–272[g]; 276[d]; 281–283[d]	138[g]; 141·5[d]; 141[a,b]; 142[a]; 143–144[d,g,d,g]
Benzene pentacarboxylic	228–230[d]; 238[b,d]; 229–234 anh. or dec.[g]	146–147[a,b]; 148·2[a]; 149–150[d,g]
Mellitic (exa)	288 c.c.[a]; 288–292[d]	187[a]; 187–188[a]; 182–184[d]; 188[a]; 186–187[d]

[11] F. González-Sánchez *Combustibles* (*Zaragoza*) **15**, 273, 361 (1955).

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their neutral methyl esters, and also to determine for both acids and esters properties hitherto unknown or not well defined, which could be used in the future for a better characterisation of these compounds. In the present paper, which is the first of a series dealing with the above objectives, the preparation and purification of the benzene carboxylic acids giving solid, neutral methyl esters and of these esters are described. Corrected m.p.s are also given for these nine solid esters.

EXPERIMENTAL

Solid, neutral, methyl esters

Starting materials for the preparation of the nine solid esters were the impure esters or the corresponding acids. When acids were used, they were dissolved in anhydrous methanol or ether or mixtures of both and esterified totally with an excess of ethereal diazomethane. Purification of the esters was accomplished by repeated crystallisation in reagent grade methanol. The esters were crystallised until constant m.p. and then, at least, three times more. Special precautions were taken to prevent contamination of samples or solutions by dust or other impurities. Elementary analyses are shown in Table 2.

Benzene carboxylic acids giving solid, neutral methyl esters

The nine benzene carboxylic acids which give solid, neutral methyl esters were prepared from the corresponding esters by acid hydrolysis, as follows: To 100 ml

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Footnotes to Table 1

[a] Phthalic anhydride melts at 131·6°C'. [b] Trimellitic anhydride melts at 162°; 163°[c,d]; 162·5–163·5°[e]; 165–167°[e]; 166°C[e]. [c] Burriel-Marti, *Bull. Soc. Chim. Belg.* **39,** 590 (1930). [d] Jessup, Green, *J. Res. Nat. Bur. Stand.* **13,** 469 (1934). [e] Schwab, Wichers, *Ibid.* **34,** 333 (1945). [f] Landolt-Börnstein, *Physikalisch-Chem. Tabellen* Erg. IIIa, Table 84. [g] (Ref. 13). [h] Graebe, Bossel, *Ann.* **290,** 206 (1896). [i] Graebe, Leonhardt, *Ibid.* **290,** 218 (1896). [j] Dziewonski, *Ber. Dtsch. Chem. Ges.* **46,** 2156 (1913). [k] Mousseron, Nguyen-Phuoc-Du, *Bull. Soc. Chim. Fr.* 91 (1948). [l] (Ref. 3). [m] Freund, Fleischer, *Ann.* **373,** 321 (1910); *Ibid.* **402,** 54 (1914). [n] Wegscheider, Perndanner, Auspitzer, *Monatsh.* **31,** 1253 (1910). [o] Fleischer, Seifert, *Ann.* **422,** 312 (1921). [p] Ekstrand, *J. Prakt. Chem.* (2), **43,** 428 (1891). [q] Ruzicka, de Graaf, Hosking, *Helv. Chim. Acta* **14** 233 (1931). [r] Mills, Nodder, *J. Chem. Soc.* **119,** 2094 (1921). [s] Morgan, Coulson, *Ibid.* 2551 (1929). [t] Maxwell, Partington, *Trans. Faraday Soc.* **32,** 775 (1936). [u] Feist, *Ann.* **496,** 102 (1932). [v] Huebner, Jacobs, *J. Biol. Chem.* **169,** 211, (1947). [w] Reppe, Sweckendiek, *Ann.* **560,** 104 (1948). [x] Fernholz, *Ibid.* **568,** 63 (1950). [y] Fusco, Palazzo, Chiavarelli, Bovet, *Gazz. Chim. Ital.* **78,** 511 (1948). [z] Graebe, Krafft, *Ber. Dtsch. Chem. Ges.* **39,** 2509 (1906). [a'] Ullmann, Uzbachian, *Ibid.* **36,** 1798 (1903). [b'] Gastaldi, Cherchi, *Gazz. Chim. Ital.* **45,** II, 251 (1915). [c'] Schorger, *J. Amer. Chem. Soc.* **39,** 2671 (1917). [d'] Sodi-Pallares, Martinez-Garza, *Arch. Inst. Cardiol. Mex.* **17,** 833 (1947). [e'] (Ref. 5). [f'] (Ref. 4). [g'] Schroeter, *Ber. Dtsch. Chem. Ges.* **57,** 2023 (1924). [h'] (Ref. 7). [i'] (Ref. 10). [j'] Doebner, *Ann.* **311,** 143 (1900). [k'] (Ref. 6). [l'] Maxwell, Partington, *Trans. Faraday Soc.* **32,** 778 (1936). [m'] (Ref. 8). [n'] Meyer, Steiner, *Monatsh.* **35,** 391, 475 (1914). [o'] Feist, *Ber. Dtsch. Chem. Ges.* **44,** 135 (1911). [p'] Fleischer, Seifert, *Ann.* **422,** 272 (1921). [q'] Schroeter, Weitzenboeck, Witt, *Monatsh.* **29,** 246, 249, 749 (1908). [r'] Wolff, *Ann.* **322,** 387 (1902). [s'] von Baeyer, *Ber. Dtsch. Chem. Ges.* **31,** 1404 (1898). [t'] Aschan, *Ann.* **387,** 1 (1911). [u'] Stark, Garben, *Ber. Dtsch. Chem. Ges.* **46,** 663 (1913). [v'] Hieber, *Ann.* **439,** 97 (1924). [w'] Schwanert, *Ibid.* **132,** 269 (1864). [x'] Mulliken, *Method* I, 85 (1904). [y'] Zelinski, Glinka, *Ber. Dtsch. Chem. Ges.* **44,** 2, 305 (1911). [z'] Cohen, Pennington, *J. Chem. Soc.* **113,** 57 (1918). [a''] Bogert, Harris, *J. Amer. Chem. Soc.* **41,** 1676 (1919). [b''] Weissberger, Williams, *Z. Physik. Chem.* (B), **3,** 367 (1929). [c''] Meyer, *Monatsh.* **25,** 1205 (1904). [d''] Meyer, Wesche, *Ber. Dtsch. Chem. Ges.* **50,** 452 (1917). [e''] Piutti, *Ibid.* **20,** 539 (1887). [f''] van der Zanden, de Vries, *Rec. Trav. Chim.* **67,** 998 (1948). [g''] Warnat, *Ber. Dtsch. Chem. Ges.* **58B,** 2768 (1925). [h''] Spath, Holter, Posega, *Ibid.* **61B,** 322 (1928). [i''] Fieser, Peters, *J. Amer. Chem. Soc.* **54,** 4347 (1932). [j''] Ruzicka, Seidel, Brugger, *Helv. Chim. Acta* **30,** 2168 (1947). [k''] Ruzicka, Brugger, Egli, Ehmann, Goldberg, *Ibid.* **15,** 1496 (1932). [l''] Campbell, Todd, *J. Amer. Chem. Soc.* **61,** 1291 (1940). [m''] Farmer, Ingold, *J. Chem. Soc.* **119,** 2001 (1921). [n''] Ruzicka, Schinz, Meyer, *Helv. Chim. Acta* **6,** 1077 (1923). [o''] Fieser, Campbell, *J. Amer. Chem. Soc.* **60,** 2635 (1938). [p''] Fischer, Schrader, Treibs, *Ges. Abhandl. Kenntnis Kohle* **5,** 259 (1920). [q''] Campbell, Soffer, Steadman, *J. Amer. Chem. Soc.* **64,** 425 (1942). [r''] Kraut, Busse, *Ann.* **177,** 273 (1875). [s''] Pechmann, *Ber. Dtsch. Chem. Ges.* **31,** 502 (1898). [t''] Diels, *Ibid.* **75B,** 1452 (1942). [u''] Fichter, Stenzl, Beglinger, *Helv. Chim. Acta* **21,** 375 (1938). [v''] Schultze, *Ann.* **359,** 129 (1908). [w''] Spath, Kuffner, *Ber. Dtsch. Chem. Ges.* **64B,** 371 (1931). [x''] Smith, Tomarelli, Howard, *J. Amer. Chem. Soc.* **61,** 2398 (1939).

of 2-3N hydrochloric acid in a 250 ml round bottom, necked flask, amounts of about 0·3–0·6 g of the purified esters, exactly weighed to the nearest 0·1 mg, were added, and the mixture boiled gently under reflux for 24 hr. Prior to removing the condenser, this was washed internally with small portions of distilled water. The contents of the flask were filtered quantitatively to a weighed 150 ml beaker. The flask was washed several times with small amounts of hot distilled water and the washings added to the beaker. The hydrochloric acid was removed on the steam bath, with addition of small portions of water to prevent concentration. After evaporation to dryness, the beaker and its content were dried to constant weight at 105°C and the amount of acid determined. No special precautions had to be taken and the acids were further purified by several recrystallisations from water or 1 : 1 hydrochloric acid. Elementary analyses of the acids are shown in Table 2.

TABLE 2. MICROANALYSES OF THE PURIFIED BENZENE CARBOXYLIC ACIDS AND NEUTRAL METHYL ESTERS

Compound	Acid				Ester			
	Carbon, %		Hydrogen, %		Carbon, %		Hydrogen, %	
	Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
1-2	57·83	57·90	3·64	3·67	61·85	61·81	5·19	5·22
1-3	57·83	57·80	3·64	3·70	61·85	61·83	5·19	5·26
1-2-3	51·44	51·46	2·88	2·89	57·14	57·19	4·80	4·79
1-3-5	51·44	51·38	2·88	2·95	57·14	57·11	4·80	4·74
1-2-3-4	47·26	47·29	2·38	2·44	54·20	54·25	4·55	4·58
1-2-3-5	47·26	47·32	2·38	2·35	54·20	54·21	4·55	4·54
1-2-4-5	41·39[a]	41·24[a]	3·47[a]	3·55[a]	54·20	54·13	4·55	4·58
Penta	44·31	44·26	2·03	2·04	52·18	52·21	4·38	4·34
Exa	42·12	42·16	1·77	1·83	50·71	50·81	4·26	4·21

[a] Analysed as hydrate ($+2H_2O$).

Melting points

These were determined in a modified Hershberg apparatus.[12] The apparatus was provided with a mechanical stirrer mounted on a ball-bearing assembly to keep the liquid moving at a rapid rate and with a Bureau of Standards, certified, total-immersion thermometer. Corrected m.p.s for the nine purified solid esters were calculated from the uncorrected ones by means of the usual formula, $\Delta = \text{K.n.}\ (T_{\text{obs.}} - t_{\text{stem}})$. Uncorrected and corrected m.p.s were determined on the purified samples and are shown in Table 3. The m.p.s observed are in general somewhat higher than those previously reported (Table 1). In particular, the m.p. of the 1-2-3-5-ester was raised from 107–111° to 115·6–116·4° (cor.), confirming recent observations of Read and Purves[10] who quoted 111–116°. Comparison of the m.p. of benzoic acid (compare

[12] E. B. Hersberg *Industr. Engng. Chem. (Anal.)* **8**, 312 (1936).

this with most exact values reported in Table 1) and the esters suggests that the lower temperatures starting the melting ranges found for the latter may possibly be the absolute m.p.s of these esters.

TABLE 3. M.P.S OF THE SOLID, NEUTRAL METHYL ESTERS

Ester	M.p., °C (uncorr.)	M.p., °C (corr.)
1-3	67·6–68·1	67·8–68·3
1-4	139·1–139·9	141·0–141·8
1-2-3	100·9–101·4	101·6–102·1
1-3-5	143·3–144·0	145·3–146·0
1-2-3-4	129·6–130·3	131·1–131·8
1-2-3-5	114·5–115·3	115·6–116·4
1-2-4-5	141·7–142·5	143·6–144·4
Penta	147·8–148·6	149·8–150·6
Exa	186·1–186·9	189·7–190·5
Benzoic acid[a]	121·2–121·9	122·4–123·1

[a] Bureau of Standards certified benzoic acid, for comparison.

As already indicated the nine benzene carboxylic acids studied have no true m.p.s. It is therefore impossible to check their purity or to follow their purification by crystallisation, by means of the melting characteristics.

In Table 4, material balances of the hydrolyses of eight of the nine esters are

TABLE 4. BALANCES OF THE HYDROLYSES

Acid	Ester hydrolysed g	Acid	
		Calc. g	Recovd. g
1-3	0·2628	0·2248	0·2248
1-2-3	0·4419	0·3682	0·3679
1-3-5	0·5665	0·4720	0·4718
1-2-3-4	0·3370	0·2761	0·2759
1-2-3-5	0·3118	0·2554	0·2549
1-2-4-5	0·5964	0·4886	0·4892
Penta[a]	0·9275	0·7509	0·7504
Exa	0·5492	0·4408	0·4404

[a] Prepared in two batches.

shown. Due to the low solubility of the terephthalic acid, the amount of ester hydrolysed was too small to permit a reliable balance; the hydrolysis was otherwise normal. Although it was difficult to visualise at first the hydrolysis of insoluble esters with m.p.s higher than the temperatures of boiling of the aqueous solutions, in practice the method developed worked out satisfactorily. Hydrolyses were complete, no side reactions, such as decarboxylation, were found and no impurities are

introduced. On examination of Table 4, it is easily seen that the differences between the amounts of acid calculated and recovered are very small and the mean deviation for the eight cases is only ±0·08%, referred to calc. acid.

Microanalyses of both the purified acids and esters are shown in Table 2. These analyses were performed by an independent laboratory. An examination of the elementary analyses of carbon and hydrogen of eighteen closely related compounds, shows that values found for both carbon and hydrogen are within ±0·08% of the calc. ones, except carbon for mellitic ester and hydrogen for pyromellitic acid which deviate, respectively, by 0·11 and −0·15%. Mean deviations among the values found and calculated are: Esters: C, ±0·046% and H, ±0·037%; Acids: C, ±0·057% and H, ±0·046%, giving an overall mean deviation of about ±0·05%. These statistical results point to a high degree of purity of the esters and acids prepared, particularly, when they are considered in conjunction with the results of the hydrolyses and with the m.p.s found. In addition to these quantitative checks, the purified products were further examined qualitatively for impurities by means of the polarizing and stereoscopic microscopes. No impurities were found. On the basis of method used, of experimental results, and of the foregoing discussion it is believed that the prepared samples of the above nine acids and their esters are of a high purity, of the order of 99·5–99·9%.

Some errors have appeared in the literature in connection with the 1-2-3-4- and 1-2-3-5-benzene carboxylic acids. Huntress and Mulliken[13] describe the 1-2-3-4-benzene tetracarboxylic acid as having a hydrate. This acid does not form any hydrate; it is the 1-2-3-5-isomer which gives a hydrate,* so that the four hydrates of this series of acids are those of the 1-2-3, 1-2-3-5, 1-2-4-5 and penta compounds. If other hydrates, such as a mono attributed to the 1-3-5-acid, exist they must be very unstable under normal conditions. This was checked by several means including infra-red and X-ray work. The benzene pentacarboxylic hydrate is a pentahydrate; the other three are dihydrates. The stability of these hydrates, except that of the pyromellitic acid and to some extent that of the hemimellitic acid, is low. It is therefore strongly recommended that the acids be examined in an anhydrous condition, except the pyromellitic acid which is difficult to dehydrate. Smith and Carlson[7] and more recently Read and Purves[10] have pointed out that the neutral, methyl ester of 1-2-3-4-benzene carboxylic acid or the acid itself develop a purple colour when exposed to light. This property has also been mentioned by Huntress and Mulliken.[13] Highly purified samples of this acid and its ester prepared from coal have been exposed to light for several years by the author without developing a purple colour. The change in colour observed by those workers may probably be caused by some impurity being produced in their particular synthesis and which is difficult to eliminate on purification.

Acknowledgements—This paper is based partly on work performed by the author during 1951–1953 as a "Guest Fellow" at the Coal Research Laboratory, Carnegie Institute of Technology, Pittsburgh, Pa., U.S.A., on a Scholarship of the Instituto

* This error appears originally in Beilstein-IX (p. 997), where some of the properties of the 1-2-3-5-benzene carboxylic acid are described under the 1-2-3-4-isomer and vice versa. Interchange of names (and even errors) appear also in other books, abstract journals and articles as pointed out in refs. 10 and 13.

[13] E. H. Huntress and S. P. Mulliken *Identification of Pure Organic Compounds* (*Order I*) p. 121. John Wiley & Sons, Inc., New York (1941).

del Combustible of the Patronato Juan de la Cierva de Investigación Técnica of Spain. The author wishes to express his appreciation and gratitude to Dr. H. H. Lowry, Director of the Coal Research Laboratory for his encouragement and interest and to Dr. H. C. Howard of the same Laboratory, for his inspiration and helpful discussions during the work. Thanks are also due to Dr. V. Gómez Aranda, Director of the Instituto del Combustible at Zaragoza, for valuable suggestions. The ultimate microanalyses were performed by Huffman Microanalytical Laboratories, Wheatridge, Col., U.S.A.

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Tetrahedron, 1957, Vol. 1, pp. 238–240. Pergamon Press Ltd., London

OPTICAL ROTATORY DISPERSION STUDIES—XII[1]

ABSOLUTE CONFIGURATIONS OF EPERUIC AND LABDANOLIC ACIDS

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Abstract—A comparison of the rotatory dispersion curves of appropriate nor-ketones of the eperuic acid and labdanolic acid series with those of derivatives of onocerin and manool establishes the absolute configurations of these diterpene acids.

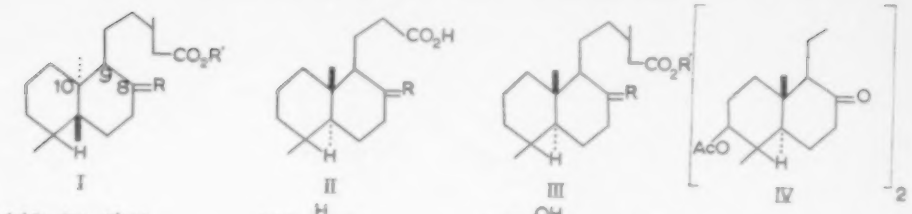
KING and Jones[2] have recently presented evidence that the diterpene eperuic acid possesses structure (Ia). No stereochemistry was assigned but it was pointed out by these authors that one of their degradation products (m.p. 134–135°, $[\alpha]_D$ − 29·9°) appeared to be isomeric with an acid (m.p. 136–137°, $[\alpha]_D$ + 33°) of the same structure (IIa) derived from ambrein.[3] The tentative inference could be drawn that these two compounds were in fact antipodes.

Shortly thereafter, Cocker and Halsall[4] established structure (IIIa) for the diterpene labdanolic acid and related it to the ambrein degradation acid (IIa). The identity of the two specimens, notably the sign of rotation, proved the absolute configuration of labdanolic acid as implied by expression (IIIa) since ambrein has been related to manool[5] and thence to the steroids and *D*-glyceraldehyde. Cocker and Halsall[4] have pointed out that there exists on the whole a remarkable similarity between the physical constants of various eperuic and labdanolic acid derivatives except for the fact that the rotations were invariably of opposite sign. The tentative conclusion was reached that these two acids are antipodes, in so far as rings A and B are concerned.

While there are a few examples known among the lower terpenes where both antipodes exist in nature, this has never been observed in the di- and tri-terpene series—all of them possessing the same absolute configuration (with respect to the C-10 angular methyl group) as the steroids. In view of the fact that rotatory dispersion measurements have led us to propose[6] that the diterpene cafestol may belong to the antipodal series, it was decided to apply our rotatory dispersion approach to the eperuic-labdanolic acid problem.

The rotatory dispersion curve of the keto ester (IIIb)[4] derived from labdanolic acid (IIIa) should be characterized by a strong negative single Cotton-effect curve[7]

[1] Paper XI, C. Djerassi *Bull. Soc. Chim. Fr.* (1957) in press.
[2] F. E. King and G. Jones *J. Chem. Soc.* 658 (1955).
[3] L. Ruzicka and F. Lardon *Helv. Chim. Acta* **29**, 912 (1946).
[4] J. D. Cocker and T. G. Halsall *J. Chem. Soc.* 4262 (1956).
[5] L. Ruzicka, O. Dürst, and O. Jeger *Helv. Chim. Acta* **30**, 353 (1947).
[6] C. Djerassi, R. Riniker, and B. Riniker *J. Amer. Chem. Soc.* **78**, 6362 (1956).
[7] For nomenclature see C. Djerassi and W. Klyne *Proc. Chem. Soc.* 55 (1957).



(a) R=CH_2 R'=H
(b) R=O R'=CH_3

(a) R=H, OH—CH_3
(b) R=O

(a) R=OH—CH_3 R'=H
(b) R=O R'=CH_3

similar to that exhibited by friedelin[6] and the mirror image of that of a 2-keto-5α-steroid.[8] That this is indeed the case is illustrated in Fig. 1 for the ester (IIIb)—R. D.[7] in dioxane (*c.* 0·094), 25°; $[\alpha]_{700}$ −18°, $[\alpha]_{589}$ −39°, $[\alpha]_{317\cdot5}$ −1440°, $[\alpha]_{277\cdot5}$ +1050°, $[\alpha]_{272\cdot5}$ +785°—and the validity of this approach is exemplified even further in

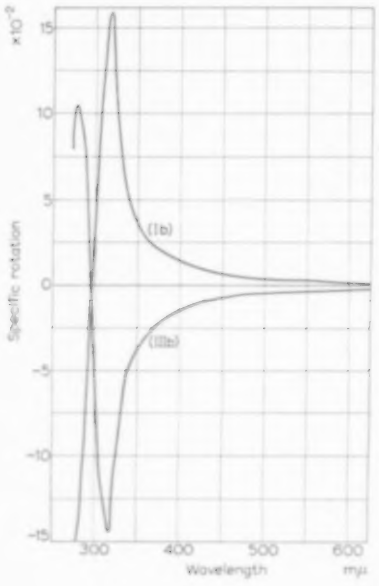


FIG. 1.

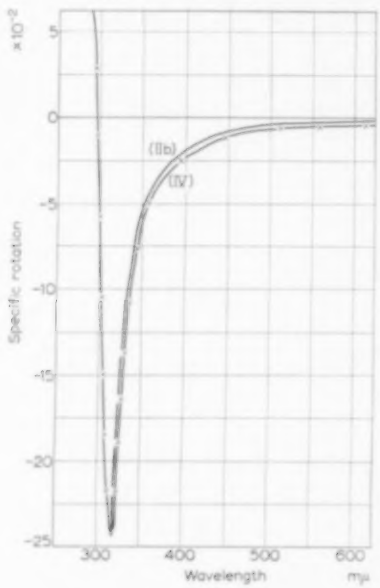


FIG. 2.

Fig. 2 where the rotatory dispersion curves of the keto acid (IIb)—R. D. in dioxane (*c.* 0·121), 25°; $[\alpha]_{700}$ −20°, $[\alpha]_{589}$ −21°, $[\alpha]_{317\cdot5}$ −2440°, $[\alpha]_{280}$ +2190°—derived[9] from manool and of bisnor-8, 13-dioxo-α-onocerane-3, 16-diol diacetate (IV)[10]—R. D. in dioxane (*c.* 0·054), 25°; $[\alpha]_{700}$ −26°, $[\alpha]_{589}$ −46°, $[\alpha]_{317\cdot5}$ −2392°, $[\alpha]_{275}$ +2472°—are reproduced. The absolute configurations of both manool and onocerin have already been established by classical chemical means[11,12] so that their rotatory dispersion curves can be used as even more precise models than those of steroids.

[8] C. Djerassi, W. Closson, and A. E. Lippman *J. Amer. Chem. Soc.* **78**, 3163 (1956).
[9] B. Riniker, Thesis, E. T. H. Zurich, 1955, p. 33. cf. H. R. Schenk, H. Gurtmann, O. Jeger, and L. Ruzicka *Helv. Chim. Acta* **35**, 817 (1952).
[10] D. H. R. Barton and K. H. Overton *J. Chem. Soc.* 2639 (1955).
[11] E. Kyburz, B. Riniker H. R. Schenk, H. Heusser, and O. Jeger *Helv. Chim. Acta* **36**, 1891 (1953).
[12] D. Arigoni and O. Jeger *Ibid.* **39**, 174 (1956).

On the other hand, the rotatory dispersion curve (Fig. 1) of the keto ester (Ib)—R.D. in dioxane (*c*. 0·113), 25°; $[\alpha]_{700}$ +6°, $[\alpha]_{589}$ +17°, $[\alpha]_{317\cdot5}$ +1585°, $[\alpha]_{280}$ −1505°—obtained[2] from eperuic acid (Ia) is virtually the mirror image of that of the corresponding labdanolic acid derivative (IIIb). It should be noted that quantitatively, the curves are not exact mirror images—as is required of antipodes—and that a fairly large discrepancy exists in the melting points (m.p. 223° *vs.* 190°) of the oximes of the keto acids corresponding to (Ib) and (IIIb). We have had occasion to repeat the preparation of these oximes under identical conditions starting with the original diterpene samples and have fully confirmed the earlier constants.[2,4*] It would appear, therefore, that there exists a slight stereochemical difference between eperuic acid and labdanolic acid, possibly isomerism at C-9. This is supported by the observation of Cocker and Halsall[4] that identical infra-red curves and rotations (but opposite in sign) are observed in the common liquid Δ^8-unsaturated methyl esters.[9]

Aside from the minor difference mentioned above, we believe that the rotatory dispersion curves of Fig. 1 clearly justify the assumption that eperuic acid[2] is the first authentic case of a diterpene with the "wrong" absolute configuration. Current work in our laboratories based on rotatory dispersion analyses seems to suggest that such terpenoids are more common than has hitherto been assumed.

Acknowledgements—We are greatly indebted to Drs. D. H. R. Barton, T. G. Halsall O. Jeger, G. Jones and F. E. King for generous gifts of samples and to the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service for financial assistance (grant No. C-2919). The rotatory dispersion measurements were carried out by Mrs. V. Halpern and Mrs. J. Osiecki.

* The keto esters (Ib) and (IIIb) exhibited identical infra-red spectra in chloroform solution, but the nujol (insol. in $CHCl_3$) spectra of the acid oximes were quite different.

Tetrahedron, 1957, Vol. 1, pp. 241–247. Pergamon Press Ltd., London

HOMOLYTIC ISOMERISATION OF 1,1,1-TRICHLORO-2-BROMOPROPENE*

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(*Received* 18 *March* 1957)

Abstract—(1) 1,1,1-trichloro-2-bromopropene has been shown to isomerise homolytically when exposed to ultra-violet light to form 1,1,2-trichloro-3-bromopropene and heterolytically under the action of antimony pentachloride to yield 1,1,3-trichloro-2-bromopropene.

(2) The bromination of 1,1,1-trichloropropene has been investigated under various conditions. It has been found, that the reaction runs unambiguously to give a normal addition product of 1,1,1-trichloro-2,3-dibromopropene only in strongly polarised media. When the reaction is being carried out in non-polarised media or in the presence of benzoyl peroxide, 1,1,2-trichloro-1,3-dibromopropane is obtained together with 1,1,1-trichloro-2,3-dibromopropane, the former being due to the homolytic isomerisation of the intermediate radical.

UNTIL recently the question whether free radicals can rearrange in solutions was subject to controversy.[1-2-3] At present a number of such rearrangements has been unambiguously proved, several cases of rearrangement by the migration of phenyl (or tolyl) according to scheme 1 being known:[4-8]

$$C_6H_5CR_2\dot{C}H_2 \rightarrow R_2\dot{C}—CH_2C_6H_5 \quad \text{where} \quad R = \text{alkyl, aryl} \tag{1}$$

Two of the present authors and Zakharkin[9] have discovered a rearrangement in the radical by the migration of chlorine, scheme 2:

$$CCl_3CHCH_2X \rightarrow \dot{C}Cl_2CHClCH_2X \quad \text{where} \quad X = Br, CCl_3 \tag{2}$$

This rearrangement has been observed when investigating the reaction of bromotrichloromethane or hydrogen bromide addition to 1,1,1-trichloropropene in the presence of benzoyl peroxide.

In the literature there are contradictory statements about the possibility of rearrangements in radicals due to the migration of the methyl group. Some authors[8,10,11] have found that the neopentyl radical does not undergo isomerisation. Kharasch *et al.*[12] are of the opinion that they did observe this type of rearrangement when brominating 2,2,4,4-tetramethylpentane, at 200°, according to scheme 3:

$$(CH_3)_3C—\dot{C}H—C(CH_3)_3 \rightarrow (CH_3)_2\dot{C}CHC(CH_3)_3 \tag{3}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad CH_2$$

* *Translated by* A. L. PUMPIANSKY, Moscow.

[1] H. Clazebrook and T. Pearson *J. Chem. Soc.* 1777 (1936).
[2] M. Kharasch, S. Kane, and H. Brown *J. Amer. Chem. Soc.* **63**, 526 (1941).
[3] M. Dewar *The Electronic Theory of Org. Chem.* p. 263. Oxford (1950).
[4] W. Urry and M. Kharasch *J. Amer. Chem. Soc.* **66**, 1438 (1944).
[5] S. Winstein and F. Seubold *J. Amer. Chem. Soc.* **69**, 2916 (1947).
[6] F. Seubold *J. Amer. Chem. Soc.* **75**, 2532 (1953).
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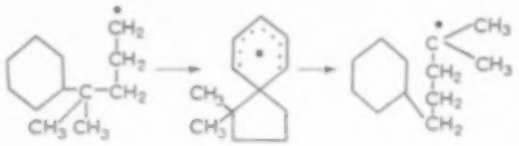
Using different procedures,[13–16] it has been shown, that rearrangements in radicals by the migration of hydrogen from the adjacent carbon atom are impossible, whilst those due to the migration of hydrogen from carbon atoms situated at a great distance appear to take place.[13]

Decarbonylation of 5-methyl-5-phenyl hexanal results in a rearrangement,[17] which is represented by scheme 4:



(4)

As far as we know, there have up to now been no detailed reports on the homolytic conversion of any compound into an isomeric one, that is on homolytic isomerisation.

We are now reporting on the homolytic isomerisation of 1,1,1-trichloro-2-bromopropene into 1,1,2-trichloro-3-bromopropene-1, according to scheme 5:

$$\underset{\text{I}}{CCl_3CBr{=}CH_2} \rightarrow \underset{\text{II}}{CCl_2{=}CCl{-}CH_2Br} \qquad (5)$$

When a sample of this compound is allowed to stand, it isomerises fully into 1,1,2-trichloro-3-bromopropene-1 after an induction period (1 or 2 days) or when exposed to ultra-violet light for several minutes, without heating. Addition of hydroquinone or dimethylaniline to 1,1,1-trichloro-2-bromopropene inhibits isomerisation, samples containing the inhibitor undergoing no change for over a month.

The isomerisation must have proceeded along the following scheme:

$$\text{a. } CCl_3CBr{=}CH_2 \rightarrow C_2H_2Cl_3^{\cdot} + Br$$

$$\text{b. } CCl_3CBr{=}CH_2 + Br \rightarrow CCl_3\dot{C}BrCH_2Br$$

$$\text{c. } CCl_3\dot{C}Br{-}CH_2Br \xrightarrow{\text{rearrangement}} CCl_2\dot{C}BrClCH_2Br \qquad (6)$$

$$\text{d. } CCl_2\dot{C}ClBrCH_2Br + CCl_3CBr{=}CH_2 \rightarrow CCl_2{=}CClCH_2Br + CCl_3\dot{C}BrCH_2Br$$

The homolytic isomerisation of $CCl_3C\,Br{=}CH_2$, is of interest in that its direction differs from that of the anionotropic allylic rearrangement of the same compound. We have shown 1,1,1-trichloro-2-bromopropene to undergo allylic rearrangement under the action of antimony pentachloride or aluminium chloride to form 1,1,3-trichloro-2-bromopropene-1. The two rearrangements are compared in scheme 7:

$$\underset{\text{I}}{CCl_3CBr{=}CH_2} \xrightarrow[SbCl_5]{h\nu} \begin{cases} \underset{\text{II}}{CCl_2{=}CCl\,CH_2Br} \\ \underset{\text{III}}{CCl_2{=}CBr\,CH_2Cl} \end{cases} \qquad (7)$$

The procedures employed to obtain the substances under investigation and to prove their structures are, briefly, as follows.

[13] R. E. Mardaleishvili Report at Lomonosov Readings, edited by Moscow State University (1953).
D. N. Kursanov and V. V. Voyevodski *Uspekhi Khimii* **23**, No. 6, 641 (1954).
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As starting compound for 1,1,1-trichloro-2-bromopropene we used 1,1,1-trichloro-2,3-dibromopropane, obtained by the action of bromine on 1,1,1-trichloropropene in acetic acid medium in the dark.

1,1,1-trichloro-2,3-dibromopropane being acted upon by potassium hydroxide in ethylcellosolve gave 1,1,1-trichloro-2-bromopropene, as a sole product, according to the following scheme:

$$CCl_3CHBrCH_2Br \xrightarrow{KOH} CCl_3CBr{=}CH_2$$

The allylic isomer of this compound—1,1,3-trichloro-2-bromopropene-1 was obtained following scheme 8:

$$CCl_2{=}CHCH_2Cl + Br_2 \rightarrow \underset{IV}{CCl_2BrCHBrCH_2Cl} \xrightarrow{KOH} \underset{III}{CCl_2{=}CBrCH_2Cl} \quad (8)$$

The structure of compound IV was ascertained by the hydrolysis with nitric acid (sp. gr. 1·52), which resulted in a high yield of α-bromo-β-chloropropionic acid, the latter yielding, when treated with alcoholic alkali, α-bromoacrylic acid.

The isomerisation of I into III under the action of $SbCl_5$ (scheme 7) suggests the structure of the former compound, for the reverse isomerisation of III into I is unknown.

1,1,2-Trichloro-3-bromopropene-1 resulting from the homolytic isomerisation of substance I (scheme 5) has been synthesised independently according to scheme 9:

$$CCl_2{=}CClCH_2Cl \xrightarrow[(CH_3)_2CO]{NaBr} CCl_2{=}CClCH_2Br \quad (9)$$

The three trichlorobromopropenes I, II and III, produced by isomerisation according to scheme 7 as well as independently according to schemes 8 and 9, were identified as crystalline hydrochlorides of their diethylamine derivatives, obtained by schemes 10 and 11:

$$\left.\begin{array}{l} CCl_3CBr{=}CH_2 + (C_2H_5)_2NH \rightarrow CCl_2{=}CBrCH_2N(C_2H_5)_2 \cdot HCl \\ CCl_2{=}CBrCH_2Cl + (C_2H_5)_2NH \end{array}\right. \quad (10)$$

$$CCl_2{=}CClCH_2Br + (C_2H_5)_2NH \rightarrow CCl_2{=}CClCH_2N(C_2H_5)_2 \xrightarrow{HCl} \underset{VI}{CCl_2{=}CClCH_2N(C_2H_5)_2 \cdot HCl} \quad (11)$$

Hydrochloride VI did not reveal any depression of the melting point on mixing with the authentic sample, obtained previously.[18] 1,1,1-trichloro-2-bromopropene (I) and its allylic isomer (III), obtained by isomerisation as well as following scheme 8, reacting with benzene in the presence of aluminium chloride, yield the same compound $C_6H_5CH_2CBr{=}CCl_2$.

One is also to mention the following observations made in the course of this work.

Two of the present authors and V. I. Firstov[19] have reported on the bromination of 1,1,1-trichloropropene, and by analogy the trichlorodibromopropane formed has been assigned the structure of 1,1,1-trichloro-2,3-dibromopropane.

The rearrangement mentioned above having been discovered[9] (see scheme 2), we

[18] R. Kh. Freidlina, V. N. Kost, and A. N. Nesmeyanov *Izv. Akad. Nauk SSSR. Otdel. khim. Nauk* 233 (1955).

[19] A. N. Nesmeyanov, R. Kh. Freidlina, and V. I. Firstov *Izv. Akad. Nauk SSSR. Otdel. khim. Nauk* 505 (1951).

were led to suggest that depending on the reaction conditions, bromination of 1,1,1-trichloropropene could proceed both without rearrangement (electrophilic addition) and with rearrangement (homolytic addition).

$$CCl_3CH{=}CH_2 + Br \rightarrow CCl_3\dot{C}HCH_2Br \rightarrow \dot{C}Cl_2CHClCH_2Br$$

$$\dot{C}Cl_2CHClCH_2Br + Br_2 \rightarrow CCl_2BrCHClCH_2Br + Br$$

The elucidation of this point seemed to be of particular importance as the reaction of bromine addition to unsaturated compounds is frequently used for ascertaining the structure and identification of unsaturated compounds.

Keeping this in mind we have undertaken the investigation of the bromination of 1,1,1-trichloropropene, the following results having been obtained.

In media, favouring ionic addition, e.g. in acetic acid or ether in the presence of HBr, the reaction between 1,1,1-trichloropropene and bromine runs unambiguously to form 1,1,1-trichloro-2,3-dibromopropane. When acting with nitric acid on pure, 1,1,1-trichloro-2,3-dibromopropane we obtained only a neutral substance containing nitrogen, whose analysis showed it to correspond to a nitrate of the composition $C_3H_3Cl_3BrNO_3$.

With potassium hydroxide in ethylcellosolve 1,1,1-trichloro-2,3-dibromopropane forms, as already mentioned, 1,1,1-trichloro-2-bromopropene, which in turn, reacts with diethylamine, yielding, as a sole product $CCl_2{=}CBrCH_2N(C_2H_5)_2$.

When the reaction is carried out in chloroform, the reaction mixture being exposed to electric light (150 W), a mixture is formed which cannot be separated by distillation, which seems to consist of 1,1,1-trichloro-2,3-dibromopropane and 1,1,2-trichloro-1,3-dibromopropane. This mixture having been hydrolysed with nitric acid (sp. gr. 1·52) we isolated α-chloro-β-bromopropionic acid in 20 per cent yield. On treating the mixture with potassium hydroxide in ethylcellosolve a mixture of bromotrichloropropenes was obtained, which we succeeded in separating into their diethylamine derivatives.

$$\left.\begin{matrix} CCl_3CHBrCH_2Br \\ CCl_2BrCHClCH_2Br \end{matrix}\right\} \xrightarrow{KOH} \left\{\begin{matrix} CCl_3CBr{=}CH_2 \\ CCl_2BrCCl{=}CH_2 \end{matrix}\right\} \xrightarrow{HN(C_2H_5)_2}$$

$$\rightarrow CCl_2{=}CBrCH_2N(C_2H_5)_2 + CCl_2{=}CClCH_2N(C_2H_5)_2$$

The yield of 1,1,2-trichloro-1,3-dibromopropane is still higher, when bromination is carried out in carbon tetrachloride solution, and heating in the presence of benzoyl peroxide.

EXPERIMENTAL

1,1,1-*Trichloro*-2,3-*dibromopropane* To a solution of 1,1,1-trichloropropene (21 g) in glacial acetic acid (20 cc), a solution of bromine (24 g) in 30 ml of acetic acid was added in small portions. After the reaction was complete, the mixture was diluted with water. The dibromide, which separated was extracted, washed with water, then with aqueous sodium carbonate, again with water and dried (calcium chloride).

Distillation gave 1,1,1-trichloro-2,3-dibromopropane. Yield 36 g (80 per cent of theory), b.p. 69°/2 mm; n_D^{20} 1·5630; d_4^{20} 2·1751 (Found: MR, 45·58. Calc. MR, 46·18).

A solution of 1,1,1-trichloro-2,3-dibromopropane (15 g) in 35 cc of nitric acid (sp. gr. 1·52) was refluxed for 20 min. The reaction gave only traces of acidic material and a neutral substance (12 g) containing nitrogen, b.p. 79–80°/2 mm; n_D^{20} 1·5240;

d_4^{20} 1,9115 (Found: C 12·63; 12·57; H 1·11; 0·89; N 4·33, 4·44. $C_3H_3Cl_3BrNO_3$ requires C 12·54, H 1·05, N 4·09 per cent).

1,1,1-*Trichloro-2-bromopropene* To 1,1,1-trichloro-2,3-dibromopropane (48 g) with cooling and stirring a solution of potassium hydroxide (10 g) in 75 cc of ethylcellosolve was added dropwise with stirring for 3 hr. After diluting with water the oil which separated was extracted, washed with water and dried over sodium sulphate. Distillation gave 1,1,1-trichloro-2-bromopropene. Yield 25 g (71 per cent of theory), b.p. 57–58°/15 mm; n_D^{20} 1·5323; d_4^{20} 1·8493 (Found: MR, 37·52. Calc. MR, 37·95).

Heating trichlorobromopropene (10 g) with diethylamine (8·5 g) in methyl alcohol (50 cc) on the water-bath for 4 hr gave $CCl_2 = CBrCH_2\ N/C_2H_5/_2$. Yield 9 g (77 per cent of theory); b.p. 59°/1 mm; n_D^{20} 1·5079, d_4^{20} 1·4060 (Found: MR, 55·33. Calc. for MR, 55·50).

(Found: C, 32·35, 32·39; H, 4·79, 4·81; N, 5·43, 5·26. $C_7H_{12}Cl_2BrN$ requires C, 32·21; H, 4·63; N, 5·36 per cent.) Hydrochloride: m.p. 144–145° (from benzene and chloroform).

(Found: C, 28·64, 28·58; H, 4·65, 4·58. $C_7H_{13}Cl_3BrN$ requires C, 28·26; H, 4·45 per cent.)

Heating 1,1,1-trichloro-2-bromopropene (15 g) with 50 cc of benzene in presence of aluminiumchloride (0·5 g) gave $C_6H_5CH_2CBr = CCl_2$. Yield 14 g (78 per cent of theory); b.p. 97–98°/2 mm; n_D^{20} 1·5840; d_4^{20} 1·5566; (Found: MR, 57·19. Calc. MR, 57·19). (Found: C, 40·80, 40·93; H, 2·56, 2·64. $C_9H_7Cl_2Br$ requires C, 40·64; H, 2·65.)

Isomerisation of 1,1,1-*Trichloro-2-bromopropene*

(a) *Allylic rearrangement in the presence of* $SbCl_5$. To 1,1,1-trichloro-2-bromopropene (10 g) $SbCl_5$ (0·2 g) was added with cooling. After two hours at room temperature the mixture was washed with dilute hydrochloric acid, then with water and dried over calcium chloride. Distillation gave 1,1,3-trichloro-2-bromopropene-1. Yield 7,5 g b.p. 81–82°/21 mm; n_D^{20} 1·5522; d_4^{20} 1·8954 (Found: MR, 37·83. Calc. MR, 37·95) with properties identical to those of trichlorobromopropene, produced by dehydrobromination of $CCl_2BrCHBrCH_2Cl$ (see below).

With benzene in the presence of aluminium chloride 1,1,3-trichloride-2-bromopropene-1 gives 1,1-dichloro-2-bromo-3-phenylpropene-1 in good yield, b.p. 97–98°/2 mm; n_D^{20} 1·5840; d_4^{20} 1·5566, identical to dichlorobromophenylpropene obtained by condensation of 1,1,1-trichloro-2-bromopropene with benzene (see above).

With diethylamine in methyl alcohol solution $CCl_2 = CBrCH_2N/C_2H_5/_2$ was obtained, b.p. 61–62°/1·5 mm; n_D^{20} 1·5085; d_4^{20} 1·4068; hydrochloride: m.p. 144–145°. The mixed melting point with the hydrochloride produced by treating 1,1,1-trichloro-2-bromopropene with diethylamine (see above) and following the scheme: $CCl_2BrCHBr—CH_2Cl \xrightarrow{KOH} CCl_2=CBr—CH_2Cl \xrightarrow{N(C_2H_5)_3} CCl_2=CBrCH_2N(C_2H_5)_2$. HCl (see above) showed no depression.

(b) *Homolytic isomerisation.* When exposed to ultra-violet light, 1,1,1-trichloro-2-bromopropene, isomerises completely into 1,1,2-trichloro-3-bromopropene-1, b.p. 78–79°/19 mm; n_D^{20} 1·5550; d_4^{20} 1·8835; (Found: MR, 38·23. Calc. MR, 37·95).

(Found: C, 15·80, 15·72; H, 0·85, 0·82 $C_3H_2Cl_3Br$ requires C, 16·06; H, 0·89 per cent.)

The structure of 1,1,2-trichloro-3-bromopropene-1 was ascertained by converting it on treatment with diethylamine into 1,1,2-trichloro-3-diethylaminopropene-1, b.p.

68°/2·5 mm, n_D^{20} 1·4885; d_4^{20} 1·1910; lit.[19] b.p. 72°/3 mm, n_D^{20} 1·4888; d_4^{20} 1·1922. The mixed melting point of the hydrochloride of this amine with the hydrochloride of an authentic specimen of 1,1,2-trichloro-3-diethylaminopropene-1 showed no depression.

1,1,2-trichloro-3-bromopropene-1 was also obtained by treating sodium bromide in acetone with 1,1,2,3-tetrachloropropene-1 and had the following constants: b.p. 79–80°/20 mm; n_D^{20} 1·5550; d_4^{20} 1·8820.

1,1,3-*Trichloro*-1,2-*dibromopropane*

To a solution of 1,1,3-trichloropropene-1 (43 g) in chloroform (50 cc) a solution of bromine (48 g) in chloroform (50 cc) was added gradually. After the reaction was complete, chloroform was removed and the residue distilled in a vacuum. 1,1,3-trichloro-1,2-dibromopropane was obtained. Yield 85 g (94 per cent of theory) n_D^{20} 1·5678; d_4^{20} 2·1874 (Found: MR, 45·64. Calc. MR, 46·18).
(Found: C, 11·71, 11·60; H, 0·98, 0·96. $C_3H_3Cl_3Br_2$ requires C, 11·80; H, 0·99 per cent.)

A solution of trichlorodibromopropane (15 g) in nitric acid (30 cc, sp. gr. 1·52) was first heated gently until the violent reaction had subsided, and then refluxed for 30 min. After dilution with water the mixture was repeatedly extracted with chloroform. The chloroform extracts were washed with aqueous sodium carbonate to remove acidic products.

After acidification of the sodium carbonate washings, the acid obtained was extracted with chloroform and dried (calcium chloride). Distillation gave α-bromo-β-chloropropionic acid. Yield 7·2 g (76 per cent of theory); b.p. 125–126°/15 mm; m.p. 43–44° lit.[20] m.p. 43°.

When treated with alcoholic solution of potassium hydroxide it gave α-bromoacrylic acid, m.p. 68–69° lit.[20] m.p. 69°.

1,1,3-*Trichloro*-2-*bromopropene*-1 was prepared by dehydrobromination of 1,1,3-trichloro-1,2-dibromopropane (70 g) carried out similarly to the dehydrobromination of 1,1,1-trichloro-2,3-dibromopropane. Purification through a column, gave 1,1,3-trichloro-2-bromopropene-1. Yield 22 g, b.p. 81–82°/21 mm; n_D^{20} 1·5522; d_4^{20} 1·8955 (Found: MR, 37·83. Calc. MR, 37·95). (Found: C, 15·82, 16·00; H, 0·88, 0·77. $C_3H_2Cl_3Br$ requires C, 16·06; H, 0·89 per cent.)

In addition dichlorodibromopropene was also obtained. Yield 13 g; b.p. 97–98°/21 mm; n_D^{20} 1·5845; d_4^{20} 2·1957 (Found; MR, 41·00. Calc. MR, 40·85).
(Found: C, 13·28, 13·40; H, 0·73, 0·75. $C_3H_2Cl_2Br_2$ requires C, 13·40; H, 0·75 per cent.)

Treatment of trichlorobromopropene as well as of dichlorodibromopropene with diethylamine in methyl alcohol solution resulted in 1,1-dichloro-2-bromo-3-diethylaminopropene-1, b.p. 65–66°/1 mm; n_D^{20} 1·5079; d_4^{20} 1·4060 (Found MR, 55·33. Calc. MR, 55·50); hydrochloride: m.p. 144–145° (from benzene and chloroform).

Reaction of 1,1,1-*trichloropropene with bromine in chloroform.*

To a solution of trichloropropene (36 g) in chloroform (50 cc) a solution of bromine (40 g) in chloroform (30 cc) was added in portions, with stirring and exposure to electric light (150 w). After removal of the solvent, the residue was distilled in a vacuum, yielding a mixture of dibromides of the structureCCl_3 CHBr—CH_2Br and

[19] L. Henry *Ber. Dtsch. Chem. Ges.* **7**, 757 (1874).

$CCl_2BrCHCl—CH_2Br$, b.p. 61–62°/1 mm; n_D^{20} 1·5637; d_4^{20} 2·1756. Yield 65 g (85 per cent of theory).

Treatment of trichlorodibromopropenes produced (15 g) with nitric acid (35 cc, sp. gr. 1·52) as described above for 1,1,3-trichloro-1,2-dibromopropane gave α-chloro-β-bromopropionic acid. Yield 2 g; b.p. 134–136°/21 mm. Dehydrobromination of the latter with potassium hydroxide gave rise to α-chloroacrylic acid, m.p. 64–65°, in a good yield, lit.[20] m.p. 65°.

Neutral products. Yield 6·5 g, b.p. 79–80°/2 mm; n_D^{20} 1·5260.

Dehydrobromination of dibromotrichloropropanes (48 g) with potassium hydroxide (10 g) in ethylcellosolve (75 cc) yielded a mixture of trichlorobromopropenes. When distilled it gave the following fractions:*

(I) 48–49°/9 mm; n_D^{20} 1·5340; d_4^{20} 1·8517. Yield 19 g

(II) 49–60°/9 mm; Yield 6 g

Residue: Yield 9 g

Fraction 1 appears to be a mixture of $CCl_3CBr=CH_2$ and $CCl_2BrCCl=CH_2$, as being treated with diethylamine in methyl alcohol solution, it gave rise to $CCl_2=CCl—CH_2N(C_2H_5)_2$, yield 3·8 g; b.p. 61–62°/2 mm; n_D^{20} 1·4890; d_4^{20} 1·1980; hydrochloride: m.p. 168–169°, lit[19] 168–169° as well as to $CCl_2=CBrCH_2N(C_2H_5)_2$, b.p. 68–69°/2 mm; n_D^{20} 1·5080; d_4^{20} 1·4060; hydrochloride: m.p. 144°.

Fraction 11 gave $CCl_2=CCl—CH_2Br$. Yield 2 g, b.p. 78–79°/19 mm; n_D^{20} 1·5550; d_4^{20} 1·8834.

Bromination of 1,1,1-*trichloropropene with bromine in carbon tetrachloride in the presence of benzoyl peroxide.* To the boiling solution of 1,1,1-trichloropropene (45 g) in carbon tetrachloride (50 cc) a solution of bromine (48 g) and benzoyl peroxide (0·5 g) in carbon tetrachloride (50 cc) was added dropwise. After distillation of the solvent, the residue was distilled in a vacuum. The reaction product distilled almost entirely at 75°/3 mm; n_D^{20} 1·5640; d_4^{20} 2·1710.

Treatment of the product (15 g) with concentrated nitric acid (35 cc, sp. gr. 1·52) gave rise to α-chloro-β-bromopropionic acid, yield 3·5 g and to a neutral substance, yield 3·8 g; b.p. 79–80°/2 mm; n_D^{20} 1·5245.

Dehydrobromination of trichlorodibromopropenes (45 g), following the procedure described above, resulted in trichlorobromopropenes, yield 16 g, b.p. 49–50°/10 mm; and in 1,1,2-trichloro-3-bromopropene, yield 3·5 g, b.p. 78–79°/19 mm; n_D^{20} 1·5550; d_4^{20} 1·8834. The mixture of trichlorobromopropenes, b.p. 49–50°/10 mm was separated and the following derivatives obtained:

$CCl_2=CCl—CH_2N(C_2H_5)_2$, yield 7 g, b.p. 61–62°/2 mm; n_D^{20} 1·4891; d_4^{20} 1·1985; hydrochloride: m.p. 168–169° and $CCl_2=CBrCH_2N(C_2H_5)_2$, yield 3 g, b.p. 68–69°/2 mm; n_D^{20} 1·5080; d_4^{20} 1·4057; hydrochloride: m.p. 144°.

* To stabilise trichlorobromopropenes during distillation hydroquinone was added both into the still and the receivers.

Tetrahedron, 1957, Vol. 1, pp. 248–252. Pergamon Press Ltd., London

THERMAL TELOMERISATION OF SILANES WITH OLEFINS*

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(*Received* 18 *March* 1957)

Abstract—(1) Thermal telomerisation reaction of methyldichlorosilane with ethylene at 260–275° and pressure of 560 atm. has been effected. The resulting mixture gave on fractionation pure compounds $CH_3SiCl_2(CH_2CH_2)_nH$, with $n = 1$–6.

(2) Thermal telomerisation reaction of trichlorosilane with ethylene has been effected at 270–285° and 200 atm. pressure. The resulting mixture gave on fractionation pure compounds $Cl_3Si(CH_2CH_2)_nH$ with $n = 1$–5.

(3) Preliminary data obtained show methyldichlorosilane and propylene also to undergo the telomerisation reaction at 260–275° and pressures of 100–120 atm.

SILICON hydrides $HSiCl_3$, $HSiBr_3$, $HSiCl_2R$, $HSiClR_2$, $RSiH_3$ are known to add to double or triple bonds of unsaturated compounds[1–11] under the action of acyl and alkyl peroxides, ultra-violet light as well as on platinum.

Reactions initiated by peroxides or irradiation appear to be of a radical character. The reaction of trichlorosilane with olefins in the presence of acetyl peroxide is suggested to proceed according to the following mechanism:[1]

$$(CH_3COO)_2 \rightarrow 2CH_3COO^{\cdot} \rightarrow CH_3^{\cdot} + CO_2$$

$$CH_3^{\cdot} + HSiCl_3 \rightarrow CH_4 + SiCl_3^{\cdot}$$

$$RCH{=}CH_2 + SiCl_3^{\cdot} \rightarrow R\dot{C}HCH_2SiCl_3$$

$$R\dot{C}HCH_2SiCl_3 + HSiCl_3 \rightarrow RCH_2CH_2SiCl_3 + SiCl_3^{\cdot}$$

The photochemical telomerisation reaction of trichlorosilane with perfluoroethylene giving a mixture of products of the composition $SiCl_3(CF_2{\cdot}CF_2)_nH$ where n varies from 1 to 3 has recently been reported, and when carried out thermally the reaction gave perfluorocyclobutane together with small quantities of organosilicon compounds.[7]

The addition of trichlorosilane to the double bond of acrylonitrile, 2-vinylpyridine

* *Translated by* A. L. PUMPIANSKY.

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and allyl cyanide in the presence of organic bases has been reported and the following ionic mechanism for these reactions has been suggested.[12,13]

$$Cl_3SiH + B \rightarrow Cl_3Si^- + BH^+$$

$$CH_2{=}CHR + Cl_3Si^- \rightarrow Cl_3SiCH_2\bar{C}HR$$

$$Cl_3SiCH_2\bar{C}HR + BH^+ \rightarrow B + Cl_3SiCH_2CH_2R$$

where B is an organic base, R = —CN, CH_2CN, N⟨⟩

Nozakura[13,14] has found tetrapyridinenickel chloride to catalyse the addition of chlorosilane to vinyltrichlorosilane, 1-octene and styrol. The addition product in each case is a mixture of 2 isomers:

$SiCl_3CH_2CH_2R$ and $CH_2{-}CH(SiCl_3){-}R$, where R = $SiCl_3$; C_6H_{13}; C_6H_5.

Thermal addition of trichlorosilane and alkylchlorosilane to olefins at 160–400° has also been reported,[3] and the authors believe the reaction proceeds through a transition state, the electron attracting silicon bonding to the methylene group of the olefin $RCH{=}CH_2$ and the chlorine atom to the adjacent carbon atom, the end product resulting from the exchange of the chlorine atom with the labile hydrogen atom of the silane.

It would be reasonable to expect that the reaction between silanes and olefins can be effected by telomerisation yielding a mixture of compounds, according to the following scheme:

$$\equiv Si{-}H + n\left(C{=}C\right) \rightarrow -Si(-C-C-)_nH$$

Carrying out this reaction under pressure with an excess of olefins appeared to favour this course of the reaction. The reactions of methyldichlorosilane, ethyldichlorosilane, triethylsilane with ethylene and propylene respectively in the presence of benzoyl peroxide or tertiary butyl peroxide at 100–140° and 100–300 atm, carried out in a stainless steel autoclave, failed, however, to give a positive result. We succeeded in carrying out telomerisation when methyldichlorosilane and trichlorosilane reacted with ethylene and methyldichlorosilane with propylene at 260–285° under pressure, compounds $CH_3SiCl_2(CH_2CH_2)_nH$, $Cl_3Si(CH_2CH_2)_nH$ and $CH_3SiCl_2(C_3H_6)_nH$ respectively having been obtained.[20]

Since dialkyldichlorosilanes and alkyltrichlorosilanes are not capable of reacting with olefins,[3] the formation of a mixture of compounds excludes the thermal reaction mechanism mentioned above. It is thus evident that the thermal reaction investigated

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TABLE 1

$(CH_3SiCl_2/CH_2CH_2/_nH)$

n	Yields (Per cent of the sum of all products).	n_D^{20}	d_4^{20}	MR Found	MR Calc.*	B.p.(°C)	B.p.(°C) lit.	Ref.	C		H		Si		Cl	
									Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
1	23·6	—				100	100	15								
2	25·6	1·4312	1·0427	43·48	43·26	147–148	147·5–148	2	35·08	35·20 35·37	7·01	7·00 7·08	16·40	16·60 16·64	41·52	41·44 40·52
3	17·7	1·4390	0·9931	52·75	52·59	91 (32 mm)	192	2	42·21	42·64 42·71	8·10	8·24 8·33				
4	13·4	1·4440	0·9761	61·83	61·88	94 (6 mm)	100–110 (20 mm)	2	47·57	47·73 47·76	8·81	9·01 9·00				
5	4·7	1·4490	0·9600	71·32	71·18	111–114 (3 mm)	—	—	51·76	51·67 51·79	9·41	9·36 9·45	11·00	11·00 10·99	27·83	27·64 27·25
6	3·8	1·4532	0·9552	80·20	80·47	124–127 (3 mm)	—	—	55·12	55·28 55·32	9·83	9·90 9·93	9·91	9·80 9·57	25·08	25·22 24·70
$n > 6$	8·5															

* Calculated refraction value has been obtained based on bond refraction data due to Vogel *et al.*[16]

by us is of a chain character. The telomerisation reaction studied in the present investigation as well as addition reactions reported in the literature are the result of a cleavage of the Si—H bond, as evidenced by the absence of this bond in the compounds obtained (the test for the Si—H bond with potassium hydroxide in water being negative). The structures of the resulting methylalkyldichlorosilanes and alkyltrichlorosilanes are also substantiated by the determination of the molecular refraction of these compounds and the formation of corresponding trimethyl derivatives by the Grignard reaction.

The preliminary data concerning the reaction between methyldichlorosilane and propylene showed that the reaction is complicated; the fractional distillation of the mixture from the reaction gave fractions boiling over a range of 10–20° from which methyl alkyldichlorosilanes, n=1–3, were isolated, the structures of which were not investigated.

The yields, both of methylalkyldichlorosilanes and of alkyltrichlorosilanes of different molecular weight exhibit a regularity characteristic of the telomerisation reaction, namely, compounds with $n = 2$ were obtained in a maximum yield, that of other compounds decreasing with increasing n, amounting for $n = 5$ to 4–4, 5 per cent of the reaction products.

The reaction of methyldichlorosilane with ethylene was carried out in a 500 cm³ stainless autoclave. After CH_3SiCl_2H(123 g) had been fed into the autoclave and air driven out by nitrogen, ethylene was introduced. The reaction mixture was heated up to 260°, pressure rising to 560 atm. The reaction was maintained at 260–270° for 2 hr, pressure dropping to 50 atm. After three runs the reaction products were collected and subjected to fractional distillation, the overall feed amounting to 381 g of methyldichlorosilane yielding 499 g of reaction products. Distillation gave 51 g of recovered methyldichlorosilane. The reaction products were fractionated in a Vigreux column to give pure methylalkyldichlorosilanes $CH_3SiCl_2(CH_2CH_2)_nH$, with $n = 1$–6, their properties and yields being summarised in Table 1.

The reaction of trichlorosilane with ethylene was carried out at 270–285° for 2 hr with the maximum pressure of 200 atm. Four runs yielded 353 g of reaction product, the overall feed of trichlorosilane being 261 g. The reaction product was

TABLE 2

$(SiCl_3(CH_2CH_2)_nH)$

n	Yield (grams)	Yield (per cent to the sum of all products)	n_D^{20}	d_4^{20}	MR Found	MR Calc.	B.p. (°C)	B.p.(°C) lit	Ref.	Si Found	Si Calc.
1	69	20·1					98	97–100	(17)		
2	87	25·3	1·4352	1·1577	43·19	42·82	146–147	147–151	(18)	14·72 14·45	14·65
3	54	15·4	1·4440	1·1094	52·51	52·12	87–89/30	127/38	(19)	12·83 12·59	12·78
4	45	13·1	1·4490	1·0744	61·76	61·41	96·5/10	119/28 231–232/731	(19)	11·26 11·67	11·33
5*	14	4·0	1·4547	1·0501	71·17	70·71	76/2	183/84	(19)	10·55 10·58	10·17
$n > 5$	42	12·2									

* For $SiCl_3C_{10}H_{21}$ Calculated C—43·56 per cent H—7·67 per cent Cl—38.62 per cent
Found C—43·68 per cent H—7·79 per cent Cl—38·21 per cent
43·71 per cent 7·71 per cent 38·03 per cent

TABLE 3

n	Formula*	B.p.°/mm	n_D^{20}	d_4^{20}	MR Calc.	MR Found	C		H		Si	
							Calc.	Found	Calc.	Found	Calc.	Found
1	$C_4H_9Si(CH_3)_3$	114°	1·4030	0·7203	44·14	44·12	64·66	64·44 64·47	13·85	13·83 13·87	21·57	21·29 21·46
2	$C_6H_{13}Si(CH_3)_3$	163°	1·4160	0·7412	53·35	53·58	68·30	68·48 68·28	14·01	14·02 14·02	17·73	17·56 17·61
3	$C_8H_{17}Si(CH_3)_3$	75°/10 mm	1·4242	0·7646	62·58	62·21	70·89	71·03 71·14	14·07	14·03 14·18	15·05	14·59 14·53

* For literature values see reference.[19]

distilled on a column (15 theoretical plates), 10 g of the starting trichlorosilane being isolated. The mixture on fractionation produced pure alkyltrichlorosilanes $SiCl_3(CH_2CH_2)_nH$, with $n = 1$–5, their properties and yields being listed in Table 2. The properties of trimethyl derivatives produced from our alkyltrichlorosilanes by Grignard reaction are given in Table 3.

TABLE 4

$(CH_3SiCl_2(C_3H_6)_nH)$

n*	n_D^{20}	B.p. (°C)	Si	
			Found	Calc.
1	1·4240	123–124*†		
2	1·4400	82 (32 mm)	14·01 14·07	14·10
3	1·4540	80–82 (2mm)	11·77 11·82	11·64

* Products with $n > 3$, amounting to 10 per cent of the sum of all products, have also been obtained.
*† Literature 3: b.p. 123–124°.

The reaction of methyldichlorosilane with propylene was carried out at 260–275° for 3 hr (maximum pressure being 100 atm). Two runs yielded 216 g of reaction products with 151 g overall feed of methyldichlorosilane. Distillation of the mixture yielded 21 g of recovered methyldichlorosilane and resulted in methylalkyldichlorosilanes $CH_3SiCl_2(C_3H_6)_nH$ with $n = 1$–3; the properties of methylalkyldichlorosilanes produced from propylene are given in Table 4.

Tetrahedron, 1957, Vol. 1, pp. 253–258. Pergamon Press Ltd., London

SYNTHÈSE DU 2,3-DIMÉTHYL-D-LYXOSE

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(*Received* 25 *May* 1957)

VOL. 1 1957

Abstract—2,3-dimethyl-D-lyxose (VIII m.p. 116–117°) has been synthesised from lyxose according to "Schéma A" p. 254. and its structure confirmed by oxidation with periodic acid. The product obtained by degradation of 3,4-dimethyl-galactosamine with ninhydrin has been shown to be indistinguishable, by paper chromatography, from synthetic 2,3-dimethyl-D-lyxose.

Résumé—Le 2,3-diméthyl-D-lyxose a été synthétisé à partir du lyxose suivant le schéma A p. 254. La structure de ce dérivé a été confirmée par oxydation à l'acide périodique. En chromatographie sur papier, le 2,3-diméthyl-D-lyxose migre à la même vitesse que le produit obtenu par dégradation de la 3,4-diméthyl-D-galactosamine au moyen de ninhydrin.

UNE méthode d'identification des hexosamines basée sur la séparation chromatographique des pentoses résultant de la dégradation des 2-déoxy-2-aminohexoses par la ninhydrine a été décrite précédemment.[1]

En vue d'appliquer cette méthode à l'identification des hexosamines partiellement méthylées, libérées au cours de l'hydrolyse des mucopolysaccharides perméthylés, nous étudions actuellement les réactions de dégradation par la ninhydrine des méthylglucosamines et des méthylgalactosamines en méthylarabinoses et méthyllyxoses correspondants.

Les dérivés partiellement méthylés du lyxose étant inconnus, nous avons entrepris de les synthétiser afin d'examiner leur comportement chromatographique et de les comparer aux produits de dégradation des galactosamines méthylées de synthèse.[2]

D'autre part, la dégradation à la ninhydrine a été utilisée par K. Meyer et coll.,[3] conjointement à une réduction par l'hydrure de sodium-bore, pour transformer des disaccharides du type glucuronido-hexosamine tels que l'acide hyalobiuronique et la chondrosine en glucosido-arabinose et glucosido-lyxitol respectivement. La structure de ces disaccharides fonctionnellement plus simple a été déterminée par ces auteurs, soit par comparaison avec un produit de structure connue, soit par oxydation au periodate.

Il est possible d'envisager une application plus générale de ce procédé de dégradation intéressant, pour l'étude de la constitution d'oligosaccharides contenant des hexosamines et dans lesquels la fonction réductrice du sucre-aminé est libre, en déterminant la structure des glucosido-pentoses résultants, par la méthode classique de perméthylation. Dans le cas particulier de la galactosamine, les dérivés méthylés du lyxose pourront être utiles comme substances de référence.

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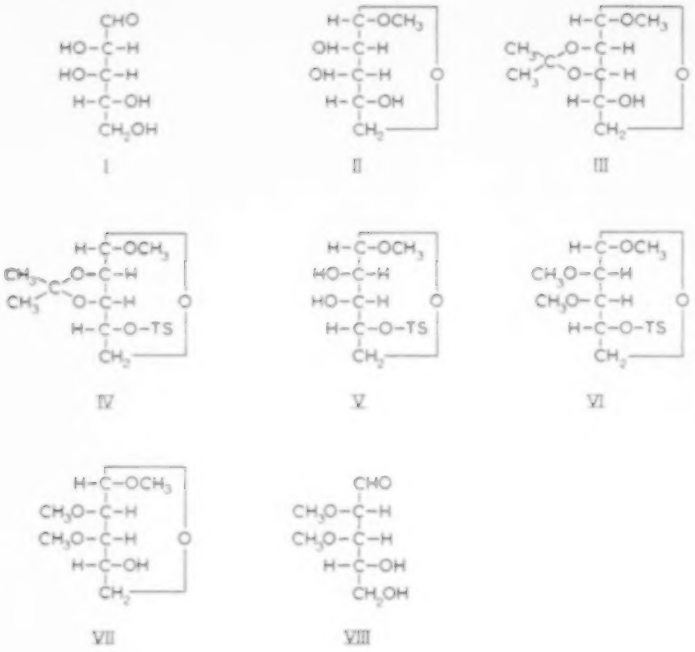
Schéma A



Remarque: TS = $-SO_2-C_6H_4-CH_3$ *p*. (Tosyl)

Dans cette communication, nous décrirons la synthèse du 2,3-diméthyl-D-lyxose à partir du méthyl-4-tosyl-D-lyxopyranoside[4] d'après le schéma A.

La méthylation du méthyl-4-tosyl-D-lyxopyranoside (4) par la méthode de Purdie-Irvine a donné le méthyl-2,3-diméthyl-4-tosyl-D-lyxopyranoside. Par réduction au moyen d'amalgame de sodium dans l'alcool, le groupe *p*. toluènesulfonyle a été éliminé et l'hydrolyse acide du méthyl-2,3-diméthyl-D-lyxopyranoside (VII) nous a permis d'obtenir le 2,3-diméthyl-lyxose (VIII) cristallin La structure du 2,3-dimethyl-lyxose a été confirmée par oxydation à l'acide périodique. Le produit consomme l'acide periodique très lentement (0,7 môle après 60 heures) avec libération d'aldéhyde formique caractérisée par précipitation à la dimédone.

En chromatographie sur papier, le 2,3-diméthyl-D-lyxose migre à la même vitesse que le produit obtenu par dégradation de la 3,4-diméthyl-D-galactosamine au moyen de ninhydrine. Les chromatogrammes ont été élués par un mélange butanol-éthanol-eau (4:1:5) et révélés par le chlorhydrate de *p*. anisidine et le phtalate acide d'aniline qui donnent des colorations identiques pour le produit synthétique et le produit de dégradation.

PARTIE EXPÉRIMENTALE[a]

Au moment où nous avons commencé ce travail nous n'avions pas connaissance de la synthèse de méthyl-4-tosyl-D-lyxopyranoside (V) réalisée par Kent et Ward.[4]

[a] Par. J. V.

[4] P. W. Kent et P. V. Ward *J. Chem. Soc.* 416 (1953).

Les constantes physiques des produits que nous avons isolés étant parfois différentes de celles rapportées par ces auteurs, nous donnons ici la description de nos expériences.

Methyl-D-lyxopyranoside (II)

A partir de 16 g de lyxose (I) préparé par dégradation de galactonate de calcium[5] et traité dans les conditions habituelles par le méthanol chlorhydrique, nous avons obtenu 14,25 g de méthyl-D-lyxopyranoside.

Méthyl-2,3-isopropylidène-D-lyxopyranoside (III)

Une solution de 14 g de méthyl-D-lyxopyranoside dans 70 ml d'acétone est ajoutée à une suspension de (II), 9 g de pentoxyde de phosphore dans 70 ml d'acétone. Le mélange est agité vigoureusement pendant 15 minutes à la température ordinaire puis décanté sur filtre. La solution est neutralisée par un excès de carbonate de potassium anhydre puis filtrée sur une double couche de Celite-Norite et le solvant est évaporé sous vide. Le sirop résiduel est extrait par plusieurs portions de chloroforme et la solution filtrée est concentrée sous vide. Le résidu sirupeux cristallise après 3 jours. Par recristallisation dans un mélange de benzène et d'hexane on obtient 11,37 g de méthyl-2,3-isopropylidène-D-lyxopyranoside sous forme de petites aiguilles incolores fondant à 49–52°.

Rendement 61 %. $[\alpha]_D^{20} = +45,6°$(EtOH c. 0,91) Trouvé: C 52,9; H 8,0. Calculé pour $C_9H_{16}O_5$(204,2): C 52,9; H 7,9 %.

A partir de 2,82 g de sirop provenant des eaux-mères, nous avons encore isolé 3,03 g de méthyl-2,3-isopropylidène-D-lyxopyranoside, ce qui porte le rendement à 75 %.

Méthyl-2,3-isopropylidène-4-tosyl-D-lyxopyranoside (*IV*)

8,0 g de méthyl-2,3-isopropylidène-D-lyxopyranoside dissous dans 40 ml de pyridine anhydre sont ajoutés à une solution de 8,5 g de chlorure de *p.* toluènesulfonyle dans 40 ml de pyridine. Le mélange est gardé pendant 50 h à la température du laboratoire puis additionné progressivement à 200 g de glace. Le méthyl-2,3-isopropylidène-4-tosyl-D-lyxopyranoside qui cristallise, est recueilli sur filtre et lavé à l'eau glacée. On en obtient 12,99 g fondant à 102–103°. Rendement 92,5 %. Après recristallisation dans le méthanol, le produit se présente sous forme de petites aiguilles incolores de p.f. 105–106°. $[\alpha]_D^{20} = -18,28°$ (EtOH c. 0,91). Trouvé: C 53,8; H 6,3; S 8,9. Calculé pour $C_{16}H_{22}O_7S$ (358,3): C 53,6; H 6,2; S 8,9 %.

Méthyl-4-tosyl-D-lyxopyranoside (V).

Une solution de 9,2 g de méthyl-2,3-isopropylidène-4-tosyl-D-lyxopyranoside (p.f. 105–106°) dans 380 ml d'acide acétique glacial est chauffée a 100° au bain marie et 180 ml d'eau sont ajoutés progressivement en 30 minutes. Le solvant est évaporé sous vide et le sirop résiduel cristallise après une nuit. Par recristallisation dans un mélange d'isopropanol et d'hexane, on obtient 6,2 g de méthyl-4-tosyl-lyxopyranoside sous forme de petites aiguilles incolores fondant à 94–95°. Rendement 84 %. $[\alpha]_D^{20} = +61,21°$ (chloroforme c. 0,88). Trouvé: C 49,0; H 5,7. Calculé pour $C_{13}H_{18}O_7S$ (317,3): C 49,0; H 5,8 %.

[5] G. Fletcher, W. Diehl, et C. S. Hudson *J. Amer. Chem. Soc.* **72**, 4546 (1950).

Méthyl-2,3-diméthyl-4-tosyl-D-lyxopyranoside (VI)

Une solution de 400 mg de méthyl-4-tosyl-D-lyxopyranoside dans 5 ml d'iodure de méthyle et 1 ml de méthanol anhydre est chauffée à reflux pendant 24 h en présence de 2 g d'oxyde d'argent fraîchement préparé. La suspension est filtrée sur Celite, le résidu solide est lavé par le méthanol chaud et le filtrat est concentré sous vide. Le résidu sirupeux, repris dans 5 ml d'iodure de méthyle est à nouveau chauffé à reflux pendant 24 h en présence de 2 g d'oxyde d'argent. Ce traitement est répété une troisième fois. Le produit final sirupeux pesant 250 mg est purifié par chromatographie sur 10 g de silice. L'élution par des mélanges de benzène-éther 9:1 et 4:1 donne 206 mg de sirop incolore. $\alpha[]_D^{20} = +32{,}0°$ (chloroforme c. 0,97) Trouvé: C 51,9; H 6,5; $-OCH_3$ 17,83. Calculé pour $C_{15}H_{22}O_7S$ (346,3): C 52,0; H 6,4; $-OCH_3$ 17,93%.

A partir de 5,80 g de méthyl-4-tosyl-D-lyxopyranoside, traité dans les mêmes conditions, 4,50 g de méthyl-2,3-diméthyl-4-tosyl-D-lyxopyranoside ont été obtenus. Le produit brut a été utilisé pour la préparation suivante.

Méthyl-2,3-diméthyl-D-lyxopyranoside (VII)

1 g de méthyl-2,3-diméthyl-4-tosyl-D-lyxopyranoside en solution dans 40 ml de méthanol à 90% est agité pendant 24 h à la température ordinaire avec 24 g d'amalgame de sodium à 2,5%. La solution séparée du mercure est neutralisée par un courant d'anhydride carbonique et filtrée. Le filtrat est concentré sous vide et le résidu d'évaporation est extrait trois fois au chloroforme. Les extraits rassemblés, filtrés et concentrés sous vide, laissent un résidu sirupeux pesant 560 mg. 211 mg de ce produit sont chromatographiés sur 10 g de silice. 145 mg de méthyl-2,3-diméthyl-D-lyxopyranoside sont élués avec un mélange d'éther et d'acétate d'éthyle dans les proportions 9:1 et 4:1. Le produit étant volatil à 100° sous vide, l'échantillon analytique est séché sous vide à la température ordinaire. $[\alpha]_D^{20} = -63{,}29°$ (EtOH c. 0,94) Trouvé: C 49,0; H 8,5. Calculé pour $C_8H_{16}O_5$ (192,1): C 49,0; H 8,4%.

2,3-*diméthyl-D-lyxose* (VIII)

333 mg de méthyl-2,3-diméthyl-D-lyxopyranoside sont chauffés à 100° pendant 3 h dans 33 ml d'une solution à 5% d'acide sulfurique dans l'eau. Après refroidissement, la solution est neutralisée au carbonate de baryum, filtrée et après évaporation du solvant, le résidu est extrait trois fois au benzène chaud. Les extraits rassemblés et filtrés sont concentrés sous vide. Le 2,3-diméthyl-D-lyxose cristallise en fin d'évaporation. Après deux recristallisations dans l'acétate d'éthyle le produit fond à 116–117°. Rendement 40%; $[\alpha]_D^{20} = -10{,}66°$(eau c. 0,3) après 24 h $[\alpha]_D^{20} = -11{,}33°$. Trouvé: C 47,2; H 7,9; $-OCH_3$ 34,67%. Calculé pour $C_7H_{14}O_5$ (178,2): C 47,2; H 7,9; $-OCH_3$ 34,84%.

Anilide du 2,3-*diméthyl-D-lyxose*

100 mg de 2,3-diméthyl-D-lyxose sont dissous dans un mélange de 0,5 ml d'aniline fraîchement distillée et 3,2 ml d'éthanol absolu. La solution est chauffée à reflux pendant 4 h. Après évaporation des solvants, le dérivé cristallise spontanément. De nombreuses cristallisations dans un mélange d'éther et d'éther de pétrole sont nécessaires pour obtenir un produit ayant un p.f. constant 107–108°. Trouvé: C 61,2; H 7,9. Calculé pour $C_{13}H_{19}O_4N$ (253,2): C 61,5; H 7,6%.

PREUVE DE STRUCTURE DU 2,3-DIMÉTHYL-D-LYXOSE

(1) *Détermination de la consommation d'acide périodique*

Afin de confirmer la structure du 2,3-diméthyl-D-lyxose, nous avons oxydé ce dernier par l'acide periodique et déterminé la consommation de ce réactif. Les modes expérimentaux décrits dans la littérature n'étant pas très explicites, nous croyons bien faire en développant ici notre mode opératoire d'une manière détaillée.

A. Solutions à préparer

Solution 1: Acide periodique 0,1 N. 12,45 g $HIO_4 \cdot 2H_2O$ dans un litre d'eau distillée.

Solution 2: Bicarbonate de sodium 2 N. 16,8 g $NaHCO_3$ dans 100 ml d'eau distillée.

Solution 3: Arsénite de sodium 0,1 N. 0,50 g As_2O_3 dans 10 ml d'une solution d'hydroxyde de sodium 1 N neutralisée ensuite par de l'acide sulfurique 1 N et amenée à 100 ml par une solution saturée de bicarbonate de sodium.

Solution 4: Solution d'iodure de potassium à 20%.

Solution 5: Solution d'iode titrée (0,099 N).

B. Méthode

Dans un ballon jaugé, on dissout 89 mg de 2,3-diméthyl-D-lyxose ($0,5 \cdot 10^{-3}$ môle) dans 22 ml de la solution 1 et on complète le volume à 250 ml par de l'eau distillée. On effectue six prises de 25 ml de cette solution 0,5 h, 1 h, 1,5 h, 16 h, 16,5 h, 17 h et 60 h après l'avoir préparée.

A chacune de ces prises on ajoute:

5 ml de la solution 2; 4 ml de la solution 3; 1 ml de la solution 4.

Après avoir laissé reposer 15 minutes à la température du laboratoire, on titre à l'aide de la solution 5.

D'autre part, on prépare une solution de référence contenant:

2,2 ml de la solution 1; 5 ml de la solution 2; 4 ml de la solution 3 et 1 ml de la solution 4.

Après avoir laissé reposer pendant 15 minutes, on titre également par la solution 5.

Dans les conditions décrites ci-dessus, nous avons constaté une consommation d'acide périodique de 0,7 môle après 60 h.

(2) *Dosage de la formaldéhyde libérée par oxydation au périodate*

A. Solutions à préparer

Solution 1: Acide périodique. 2,20 g de periodate de potassium finement divisé sont dissous à chaud dans 30 ml d'acide sulfurique 1 N. On amène ensuite à 100 ml par de l'eau distillée et on maintient à 40° pour éviter la cristallisation.

Solution 2: Bicarbonate de sodium 2 N.

Solution 3: Acide chlorhydrique 2 N.

Solution 4: Arsénite de sodium 1,2 N. 11 g d'anhydride arsénieux et 9,6 g d'hydroxyde de sodium sont dissous dans 100 ml d'eau distillée. On maintient 10 minutes à l'ébullition.

Solution 5: Acétate de sodium 2 N.

Solution 6: Dimédone (5,5-diméthylcyclohexane-1,3-dione) 80 mg de dimédone par ml d'alcool éthylique à 94%.

B. Méthode

Placer dans une fiole conique de 50 ml:

10 ml de la solution 2; 6 ml de la solution 1; 20 mg de 2,3-diméthyl-D-lyxose. pH de la solution: 7,5.

Laisser reposer 17h à la température du laboratoire, ensuite ajouter en agitant: 8 ml de la solution 5 et 2 ml de la solution 6. pH de la solution: 4,5.

Maintenir 10 minutes à 100° et laisser reposer 2 h à la température du laboratoire. Recueillir sur Iéna G.4 (préalablement séché et taré). Laver deux fois avec 50 ml d'eau distillée. Sécher 1 h à 70–80°. Le dérivé caractéristique de la formaldéhyde fond à 188–190°.

C. Résultats

A partir de 20 mg de 2,3-diméthyl-D-lyxose nous avons obtenu 11 mg de précipité fondant à 188–190°, ce qui correspond à 1,1 mg de formaldéhyde libérée, soit 0,3 môle par môle de sucre.

Le vif intérêt que Monsieur le Professeur R. H. Martin a manifesté pour ce travail a été pour nous un précieux encouragement. Qu'il veuille trouver ici l'expression de notre reconnaissance. Nous remercions Melle Mireille Vorobeitchik qui a effectué les chromatographies sur papier. Nous tenons également à remercier la maison Philips et Pain pour les résines échangeur d'ions qu'elle nous a fournies gracieusement.

Tetrahedron, 1957, Vol. 1, pp. 259–268. Pergamon Press Ltd., London

VOL.
1
1957

OXIDATIVE CYCLISATION OF DIPHENYL-2 CARBOXYLIC ACID

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(*Received* 22 *May* 1957)

Abstract—The dehydrogenation of diphenyl-2 carboxylic acid to the lactone (II; R = H) has been accomplished by oxidation with chromic acid or hydrogen peroxide and its derivatives, by decomposition of the diacyl peroxide derived from this acid, and by electrolysis of its sodium salts. From the effects of several 3′-substituents (R = OMe, $NHCOCH_3$, CN, NO_2) on these reactions it has been concluded that the oxidations with chromic acid and hydrogen peroxide etc. proceed through attachment of the oxidising agent to the carboxylic group and subsequent cationoid substitution in the neighbouring ring. The free radicals (III) are believed to be intermediates in the other two cyclisations.

INTRODUCTION

DURING another investigation[1] 2-hydroxymethyldiphenyl was crystallised although it had previously only been described as an oil. In order to confirm the structure of these crystals, they were oxidised energetically with chromic acid in acetic acid. However, the product was not diphenyl-2 carboxylic acid but instead the lactone of 2′-hydroxydiphenyl-2 carboxylic acid, 3:4-benzcoumarin (II; R = H). It was then shown that diphenyl-2 carboxylic acid could be dehydrogenated by chromic acid giving more than 50% of this lactone. Being interested in the mechanism of the dehydrogenation, we have studied it qualitatively following two paths of investigation. Firstly, the dehydrogenation has been accomplished in other ways. The carboxylic acid has been treated with hydrogen peroxide under various conditions ("peracid method"). The diacyl peroxide has been prepared from the carboxylic acid and been decomposed by heat. The sodium salt of the carboxylic acid has been electrolysed. Secondly, the behaviour of a series of 3:-substituted diphenyl-2 carboxylic acids (I; R = NO_2, CN, NHAc, OMe, X = H) has been examined; the preparation of these materials and the characterisation of the lactones derived from them are discussed in the last paragraph of this introduction.

Some general comments may be useful before the detailed presentation of our results. Two possible trivial origins of the lactone are obvious. Its precursor might be fluorenone formed by the usual condensation, and indeed the lactone has been obtained from fluorenone by means of Caro's acid.[2] But chromic acid, under our conditions, does not effect this oxidation and it is unlikely that fluorenone would be produced by the other reagents which would probably be more capable of oxidising it. An additional argument against this mechanism is that the lactones produced from substituted acids always have the structure shown in the above diagram, while the isomer (V) should sometimes be produced from a fluorenone.[3] The second possibility is that oxidation at the 2′-position produces 2′-hydroxydiphenyl-2 carboxylic acid,

[1] M. A. Murray Ph.D. Thesis, Cambridge (1948).
[2] G. Wittig and G. Pieper *Ber. Dtsch. Chem. Ges.* **73**, 295 (1940).
[3] W. von E. Doering and L. Speers *J. Amer. Chem. Soc.* **72**, 5515 (1950).

which then condenses to the lactone. In the cases of the peracid and the electrolytic methods of oxidation there is good evidence to the contrary, and this explanation is inherently improbable for the electrolytic oxidation and peroxide decomposition. The chromic acid oxidation may proceed in this way and this could probably be

checked by experiments with ^{18}O, but for the present we prefer the more economical hypothesis that its mechanism is analogous to that of the peracid oxidation. We believe that in these oxidations the major, if not the entire, source of the lactone is an activated derivative (I) generated by reaction between the carboxylic acid and the oxidising agent; the cyclisation then follows the usual course of cationoid aromatic substitution with expulsion of a proton from the 2′-position. On the other hand electrolysis of the carboxylic salt or decomposition of the peroxide should produce the radical (III) from which a hydrogen atom could be displaced. These two modes of cyclisation may be regarded as variants of a fundamental process, favoured by oxidising agents of either the two-electron-transfer or one-electron-transfer types.[4] It must be emphasised that the simultaneous operation of several mechanisms, including under some conditions the two discussed at the beginning of this paragraph, cannot be excluded by qualitative experiments such as described here. At this stage it is convenient to think in terms of a single mechanism operating at one time.

The cleanest way of dehydrogenating diphenyl-2 carboxylic acid is to treat it with another carboxylic acid and hydrogen peroxide ("peracid method"). Indeed when account is taken of the recovered starting material the yield may come close to being quantitative. This is strong evidence against the intermediacy of 2′-hydroxydiphenyl-2 carboxylic acid, since some of the 4′-hydroxy isomer should be generated simultaneously and degraded to phthalic acid. It is nevertheless difficult to achieve a very

[4] R. E. Kirk and A. W. Browne *J. Amer. Chem. Soc.* **50**, 337 (1928).

high conversion of the acid into lactone because the cyclisation is slow and there is gradual destruction of the product. Oxidation in cold trifluoroacetic acid gave 63% of lactone and 15% of the starting material was recovered. This reaction was much faster than that in acetic acid and the rate in trichloroacetic acid was intermediate. Hydrogen peroxide gave a slow reaction in water but no lactone was produced in *tert*-butyl alcohol. Obviously cyclisation is promoted by acidic conditions and therefore it is probably an ionic reaction. The fact that the same lactone is produced from diphenic acid with hydrogen peroxide in acetic acid* agrees with this idea because there is a clear analogy with decarboxylation by means of acids or halogens; in each instance carbon dioxide and a proton are expelled by a cationoid reagent. Stronger evidence has been provided by oxidation under standard conditions of diphenyl-2 carboxylic acid and four 3′-substituted derivatives. The yields of lactones with the various substituents (total recovery of material in parenthesis) were: OCH_3 30(71), $NHCOCH_3$ 20(82), H 16(95), CN 7(95), NO_2 2(97). In the first two instances loss of material through destructive oxidation was also apparent in darkening of the solutions; a control experiment, with diphenyl itself showed that the benzene rings were attacked. It might be argued that the effect of a substituent is merely to encourage or hinder hydroxylation of the benzene ring in the position para to itself and that the lactone is then formed from the hydroxy-acid, but the recovery was much better in oxidations of the unsubstituted acid on a larger scale and therefore, as already mentioned, this explanation is unlikely. The probable cause of the graded series of yields is the normal effect of a substituent on cationoid substitution. A consequent deduction is that the cationoid reagent is *not* the particle (IV), although such cations have been postulated as intermediates in oxidations.[7–11] Presumably this cation would be a very energetic molecular species generated slowly from the diphenyl-2 carboxylic acid, and the neighbouring benzene ring would be substituted very efficiently. In this event the substituent would not have much influence on the rate-determining step. The results accord better with the postulate of rate-determining cyclisation of an active species generated by a series of pre-equilibria; this might well be the conjugate acid (I; $X = \overset{+}{O}H_2$) of the peracid (I; X = OH).

Chromic acid in hot acetic acid yielded almost 60% of the lactone from diphenyl-2 carboxylic acid under our best conditions. With the series of 3′-substituted acids under standardised, slightly milder conditions the yields of lactones and, in parenthesis, the total recoveries of material were: OCH_3 15(27), $NHCOCH_3$ 1(21), H 20(73), CN 8(82), NO_2 4(88). During the reactions the first two solutions turned dark green while the others remained orange. Under still milder conditions 40% of methoxy-lactone and 20% of the acetamide-lactone could be obtained. The general trend of

* It is incidentally interesting that the lactone is also a by-product in the oxidation of phenanthraquinone to diphenic acid with hydrogen peroxide in acetic acid because the corresponding lactones have already been reported as by-products in the oxidations of 3:6-dimethoxyphenanthraquinone[5] and retenequinone.[6] The simple explanation that the lactones are formed from the diphenic acids seems probable but it was earlier rejected for the first example since attempts to oxidise the diphenic acid had failed.[5]

[5] L. F. Fieser *J. Amer. Chem. Soc.* **51,** 2471 (1929).
[6] D. E. Adelson, T. Hasselstrom, and M. T. Bogert *J. Amer. Chem. Soc.* **58,** 871 (1936).
[7] J. E. Leffler *Chem. Rev.* **45,** 385 (1949).
[8] J. E. Leffler *J. Amer. Chem. Soc.* **72,** 67 (1950). cf. D. B. Denney *J. Amer. Chem. Soc.* **78,** 590 (1956).
[9] W. A. Mosher and C. L. Kehr *J. Amer. Chem. Soc.* **75,** 3172 (1953).
[10] D. Bryce-Smith *Nature, Lond.* **172,** 863 (1953).
[11] L. S. Levitt *J. Org. Chem.* **20,** 1297 (1955).

these results is similar to that in the peracid experiments, and we conclude that here again the cyclisation is essentially a cationoid substitution in the aromatic ring. Presumably the reactive intermediate is a mixed anhydride of the carboxylic acid and chromic acid, and the reaction is analogous to the well-known oxidation of alcohols through removal of proton from a chromate ester.[12]

The crystalline diacyl peroxide was prepared from diphenyl-2 carboxylic acid. On heating in either acetic acid or carbon tetrachloride at 80° during one hour it yielded 80% and 60% respectively of the lactone.* Under the same conditions 50% and 60% respectively of the nitro-lactone was obtained from the corresponding diacyl peroxide. Some 40% of the cyano-lactone was obtained from decomposition of the crude peroxide in carbon tetrachloride. These few results contrast with those from the peracid method and they suggest the operation of a free-radical mechanism.

As free radicals are usually postulated as intermediates in Kolbe electrolyses, the electrolysis of sodium diphenyl-2 carboxylate was examined. In fact the lactone was formed, and the conversion could be raised to 33% by continual extraction of the product with benzene.† In presence of caustic soda the process was slower and less efficient, but a moderate yield of the lactone was still extracted by the benzene. As sodium 2′-hydroxydiphenyl-2 carboxylate does not, of course, lactonise, the extracted lactone cannot have been produced by hydroxylation of the benzene ring and subsequent lactonisation; it must have been an oxidation product. Comparison of the behaviours of the 3′-substituted compounds was less informative about electrolysis than about the peracid and chromic acid oxidations. The material accounted for as either lactone or starting material amounted to no more than 60% of the theoretical and the experiment with the 3′-acetamido compound was unsuccessful. In this instance the principal reaction appeared to be destructive oxidation by anodic oxygen, and it was shown that *m*-acetamidobenzoic acid suffered the same fate under conditions which scarcely affected benzoic acid itself. The yield of nitro-lactone was very small but this could be explained by its insolubility in benzene and its great susceptibility to alkaline hydrolysis. The yields of methoxy- and cyano-lactones were similar to that of unsubstituted lactone under comparable conditions. While great weight cannot be attached to this evidence, it does conform with the postulate of free-radical substitution and contrasts suitably with the variation in yields from the peracid and chromic acid oxidations of these three diphenyl-2 carboxylic acids.

Evidently the dehydrogenation of diphenyl-2 carboxylic acids, which came to our notice by chance, is quite a common phenomenon occurring by at any rate two types of mechanism. The reaction is doubtless favoured by being a cyclisation, and consequently the analogies are not numerous. As already mentioned, comparable substitution in the napthhalene nucleus during decomposition of peroxides[14] and during electrolysis[15] has been observed. The closest analogy to the peracid and chromic-acid

* Phenylation of aromatic hydrocarbons through the decomposition in them of dibenzoyl peroxide has been fully studied.[13] Benzoyloxylation may be an important, or even dominating, competitor, for example with naphthalene derivatives.[14]

† Likewise α-naphthyl acetate is a product of the electrolysis of sodium acetate in presence of naphthalene.[15]

[12] F. Holloway, M. Cohen, and F. H. Westheimer *J. Amer. Chem. Soc.* **73**, 65 (1951); and literature cited therein.
[13] D. H. Hey *J. Chem. Soc.* 1974 (1952).
[14] R. L. Dannley and M. Gippin *J. Amer. Chem. Soc.* **74**, 332 (1952).
[15] R. P. Linstead, B. R. Shephard, and B. C. L. Weedon *J. Chem. Soc.* 3624 (1952).

cyclisations is apparently the reaction between silver bromide dibenzoate and aromatic compounds;[16] benzoic esters are among the products and this mode of reaction has been classified as an electrophilic substitution, largely on account of the orientation phenomena for example the formation of *m*-nitrophenyl benzoate from nitrobenzene. Aryl benzoates are also produced by the action of halogens on silver benzoate in presence of aromatic compounds.[17, 18] It has incidentally been reported that the action of bromine on silver diphenate does not give 2:2′-dibromodiphenyl.[19] Another set of reactions, which may be connected with our chromic acid oxidations although less directly, is that leading to γ-lactones from branched-chain aliphatic acids through the action of permanganate or manganate.[20] As the reaction conditions are alkaline, the actual product is the γ-hydroxy acid, but it is likely that the lactone is the primary product in at least some instances. It has been shown[21] that there is probably more than one mechanism operating and it is unlikely that cationoid substitution, such as we postulate to explain our results, would occur at an aliphatic carbon atom. Nevertheless lactonisation in the aliphatic series may be connected with that in the aromatic to the extent that the oxidising agent is attached to the carboxyl group instead of attacking the hydrogen atom on the tertiary carbon atom, as previously suggested.[21]

The main source of our starting materials, apart from diphenyl-2 carboxylic acid itself, was the Gomberg reaction between *m*-nitrobenzene diazoacetate and methyl benzoate, which gave a mixture, separable by chromatography, of the methyl 3′-nitrodiphenyl-2 and -4 carboxylates. The preparation of the other 3′-substituted diphenyl-2 carboxylic acids from the nitro compound followed standard methods. An attempted unambiguous synthesis of this nitro compound was based on the reaction between *m*-nitrobenzylidene malonic ester and butadiene;[22] it failed at the final step of dehydrogenation.

During the foregoing discussion it has been assumed throughout that structure (II) represents all the lactones, although in principle oxidation could also have occurred *ortho* to the substituent R. In fact each oxidation seemed to produce an overwhelming proportion of one lactone and these products, with the exception of the cyano-lactone, could be correlated with the phenylazo-lactone (II; R = $N_2C_6H_5$). The structure of this substance rests on its preparation by azocoupling of the disodium salt of 2′-hydroxydiphenyl-2 carboxylic acid and on its behaviour as a normal lactone. 2′-Hydroxy-3′-phenylazodiphenyl-2 carboxylic acid should be hindered from lactonisation by hydrogen-bonding between the hydroxy and azo groups, and indeed this was found to be true of the 3′:5′-bis compound formed by coupling with excess diazonium salt.

EXPERIMENTAL*

Gomberg Reaction between m-Nitrobenzene Diazoacetate and Methyl Benzoate

A solution of *m*-nitroaniline (50 g) in concentrated hydrochloric acid (140 c.c.) and water (75 c.c.) was cooled in ice and diazotised with sodium nitrite (30 g) in water

* All m.p.s. are corrected.

[16] D. Bryce-Smith and P. Clarke *J. Chem. Soc.* 2264 (1956).
[17] L. Birkenbach and K. Meisenheimer *Ber.* **69**, 723 (1936).
[18] C. Prévost and J. Wiemann *Compt. Rend.* **204**, 989 (1937).
[19] F. Bell and I. F. B. Smyth *J. Chem. Soc.* 2372 (1949).
[20] J. Kenyon and M. C. R. Symons *J. Chem. Soc.* 2129 (1953); and literature cited therein.
[21] J. Kenyon and M. C. R. Symons *J. Chem. Soc.* 3580 (1953).
[22] K. Alder and H. F. Rickert *Ber. Dtsch. Chem. Ges.* **72**, 1983 (1939).

(60 c.c.). The diazonium solution was stirred with methyl benzoate (1 l.) at 0° while a solution of hydrated sodium acetate (140 g) in water (350 c.c.) was added. Stirring was continued for 2 days (at room temperature after the first 3 hr). The organic layer was then evaporated, finally at 100°/1 mm, to a brown tar (80 g) ,which was taken up in dry benzene and percolated through a column of active alumina (1 kg). The column was washed with benzene. Some methyl benzoate, which had remained in the tar, was soon followed in the eluate by *methyl 3'-nitrodiphenyl-2 carboxylate* (14 g, 15%), which had m.p. 94–95° after recrystallisation from methanol (Found: C, 65·8; H, 4·2; N, 5·6. $C_{14}H_{11}O_4N$ requires C, 65·4; H, 4·3; N, 5·4%). Later fractions contained *methyl 3'-nitrodiphenyl-4 carboxylate* (12 g, 13%), which had m.p. 147–148° after recrystallisation from methanol (Found: C, 65·2; H, 4·3; N, 5·5%).

Alkaline hydrolysis of the latter ester yielded the relatively insoluble *3'-nitrodiphenyl-4 carboxylic acid*, having m.p. 311–313° (decomp.) after recrystallisation from ethanol or acetic acid (Found: C, 63·8; H, 3·6; N, 5·6. $C_{13}H_9O_4N$ requires C, 64·2; H, 3·7; N, 5·8%). For structural determination this nitro-acid was reduced by adding its solution in hot dilute ammonia to warm ammoniacal ferrous sulphate solution. The hydrochloride of the amino-acid crystallised in needles when the filtered reduction solution was acidified with concentrated hydrochloric acid and cooled. One portion of the hydrochloride was oxidised with potassium permanganate in boiling sodium carbonate solution during 40 minutes; dimethyl terephthalate, m.p. 138–140°, was obtained by esterification of the acidic product with methanol and sulphuric acid. Another portion of the amino-acid hydrochloride was suspended in dilute hydrochloric acid and diazotised. The diazonium solution was kept overnight with excess hypophosphorous acid. The insoluble product was purified through recrystallisation of its sodium salt from water; it was diphenyl-4 carboxylic acid, m.p. 224–226°.

Derivatives of Diphenyl-2 Carboxylic Acid

Hydrolysis of the methyl ester with boiling 10% sodium hydroxide solution afforded *3'nitrodiphenyl-2 carboxylic acid*, m.p. 155–157°, recrystallised from aqueous acetic acid (Found: C, 64·1; H, 3·4; N, 5·7. $C_{13}H_9O_4N$ requires C, 64·2; H, 3·7; N, 5·8%). This acid had partition coefficient 1·50 between ethyl acetate and potassium phosphate solution (0·7M K_2HPO_4, 0·3M KH_2PO_4) while benzoic acid had coefficient 0·25. Consequently counter-current distribution in this system after saponification of the crude ester was an alternative method for isolating the nitro-acid from the Gomberg reaction.

Hydrogenation of the nitro-acid in ethanol with Adams platinum catalyst at room temperature and pressure furnished 3'-aminodiphenyl-2 carboxylic acid, which crystallised from alcohol and had m.p. 174–176°. The amino-acid was used directly for further experiments. Acetylation with a hot mixture of equal parts of acetic anhydride and acetic acid yielded *3'-acetamidodiphenyl-2 carboxylic acid*, m.p. 185–187°, recrystallised from water (Found: C, 70·5; H, 5·2; N, 5·7. $C_{15}H_{13}O_3N$ requires C, 70·6; H, 5·1; N, 5·5%). The amino-acid was diazotised in dilute mineral acid and then treated in three ways. Reduction for 20 hours at 5° with 10 moles of hypophosphorous acid gave diphenyl-2 carboxylic acid, purified by dissolution in alkali and reprecipitation; identification of this acid by m.p. 109–111°, mixed m.p., and conversion by concentrated sulphuric acid into fluorenone proved the orientation of substituents in the series of derivatives. Sandmeyer treatment of the diazonium salt with cuprous cyanide gave *3'-cyanodiphenyl-2 carboxylic acid*, m.p. 156–157° after recrystallisation

from water (Found: C, 75·6; H, 4·3; N, 6·4. $C_{14}H_9O_2N$ requires C, 75·3; H, 4·1; N, 6·3%). When the diazonium salt was kept at 60° for 15 minutes, a tarry solid was precipitated. This solid was dissolved in sodium hydroxide solution and treated with dimethyl sulphate at room temperature. Isolation of the acidic product and its recrystallisation from water gave *3′-methoxydiphenyl-2 carboxylic acid*, m.p. 88–90° (Found: C, 73·9; H, 5·6. $C_{14}H_{12}O_3$ requires C, 73·7; H, 5·3%).

Oxidation of Diphenyl-2 Carboxylic Acid and its 3′ Derivatives

(*a*) *Isolation of the products*

The lactone and the un-oxidised acid were brought into either benzene or ether and then separated by extraction with sodium carbonate solution. The acid was recovered by acidification and the usual extraction with ether or benzene. The lactone left by evaporation of the original solvent was always dissolved in warm sodium hydroxide solution, which was filtered before being acidified. The lactone was then either collected directly or extracted into ether and washed with sodium carbonate solution. The substituted lactones produced by the various oxidations were identified by mixed m.p.s. with the reference samples prepared as described below.

(*b*) *Oxidations with hydrogen peroxide and its derivatives*

(*i*) *In acetic acid.* A series of comparative experiments, with the results mentioned in the Introduction, was conducted as follows. The acids (0·25 g) were dissolved in acetic acid (20 c.c.) which was kept at 90° during 5 hr. At the beginning of each hour 1 c.c. of 30% hydrogen peroxide was added. The reaction mixtures were concentrated under reduced pressure before isolation of the products. Diphenyl-2 carboxylic acid itself gave 16% of the lactone and 79% was recovered under these conditions. On a preparative scale more material was accounted for. For example, when 5·45 g of acid was oxidised similarly with only 30 c.c. of hydrogen peroxide the yield of lactone, m.p. 86–88°, was 14% and the recovery of acid, m.p. 109–110°, was 86%. Under similar conditions, diphenic acid gave 3% of the same lactone while 95% was recovered, and 1% of lactone and 77% of diphenic acid were obtained from phenanthraquinone.

(*ii*) *In trifluoroacetic acid.* Hydrogen peroxide (0·18 c.c. of 86%) was added to a solution of diphenyl-2 carboxylic acid (1·06 g) in trifluoroacetic acid (5 c.c.), and the mixture was kept at room temperature overnight. The yield of lactone was 0·67 g (63%), while 0·16 g (15%) of the acid was recovered. Lower yields were obtained under a variety of conditions. Although the lactone was not rapidly destroyed at room temperature, it was preferable to avoid a large excess of hydrogen peroxide. When 30% hydrogen peroxide was used the reaction was slower. Experiments in which the acid was dissolved in methylene chloride and treated with trifluoroacetic anhydride and 86% hydrogen peroxide, were much less successful and dark coloured by-products were formed.

(*iii*) *In trichloroacetic acid.* Hydrogen peroxide (2·5 c.c. of 30%) was added to a solution of diphenyl-2 carboxylic acid (0·15 g) in trichloroacetic acid (10 c.c.). When the solution had been heated at 95° for 2 hr, 33% of lactone could be isolated.

(*iv*) *In water.* A suspension of diphenyl-2 carboxylic acid (0·15 g) in hydrogen peroxide (10 c.c. of 30%) was kept at 95° for 2 hr. The yield of lactone was 5% and 90% of the acid was recovered.

(*c*) *In* tert-*butanol.* Diphenyl-2 carboxylic acid was 92% recovered after its solution in *tert*-butanol had been boiled for 5 hr with 30% hydrogen peroxide, and no lactone could be detected.

(*c*) *Oxidation with chromic acid*

A series of comparative experiments, with the results mentioned in the Introduction, was conducted as follows. Chromic anhydride (0·3 g) was dissolved in water (1 c.c.) and added to a solution of the acid (0·1 g) in acetic acid (2 c.c.). The mixture was kept at 100° during 30 min and then it was poured into water. A better yield (50%) of the unsubstituted lactone was obtained by heating together at 100° for 45 min solutions of diphenyl-2 carboxylic acid (10 g) in acetic acid (150 c.c.) and of chromic anhydride (40 g) in water (75 c.c.); 20% of the acid was recovered.

(*d*) *Anodic oxidations*

These were carried out in a cylindrical vessel (capacity 150 c.c.), fitted with a pair of smooth platinum electrodes (surface area 0·8 cm^2; 0·2 cm apart) surrounded by a glass cooling coil. The solution was continually stirred and extracted with benzene supplied from a boiler and drawn off through a side-arm into the boiler. For comparative experiments the acids (0·3 g) were dissolved in water (100 c.c.) containing sufficient sodium carbonate for the cell to conduct 0·6 A with 60 V applied. Electrolysis was continued for 1 hr at 18°, the current being maintained at 0·6 A by steady reduction of the voltage to about 35 V. The lactone was isolated from the benzene extract while the aqueous solution was worked up for unchanged acid. The yields of lactones and acids from the 3′-substituted-diphenyl-2 carboxylic acids were: OCH_3 21 and 37, $NHCOCH_3$ 0 and 16, H 19 and 35, CN 15 and 46, NO_2 2 and 44. When *m*-acetamidobenzoic acid and benzoic acid were electrolysed under similar conditions the recoveries of them were 25% and 95% respectively. When diphenyl-2 carboxylic acid (0·645 g) was dissolved in 0·5 N sodium hydroxide only 5 V were applied in order to pass 0·6 A. During 2 hr 0·014 g (2·2%) of lactone was extracted by the benzene while 0·570 g (88·5%) of the acid was recovered. Electrolysis of a similar solution of the lactone itself in sodium hydroxide yielded no lactone in the benzene extract although 30% was recovered on acidification of the aqueous solution. Electrolysis of diphenyl-2 carboxylic acid in sodium carbonate on this scale during 2 hr gave 33% of lactone and 12% of the acid was recovered.

Decomposition of the Diacyl Peroxides

(*a*) *Diphenyl-2 carboxylic acid* (5 g) and thionyl chloride (7 c.c.) were warmed for 1 hour. The brown residue from evaporation of the thionyl chloride was dissolved in *cyclo*hexane (20 c.c.) and added to a solution of sodium peroxide (1·2 g) in water (20 c.c.) at 0°. The mixture was stirred for 30 min and then kept overnight. Colourless *bis*(*diphenyl-2-carbonyl*) *peroxide* separated and was recrystallised from aqueous acetone in plates, m.p. 107–108° (slight explosion) (Found: C, 79·4; H, 5·0. $C_{26}H_{18}O_4$ requires C, 79·2; H, 4·6%). A solution of the peroxide (0·34 g) in acetic acid (10 c.c.) was kept at 80° during 1 hr and then evaporated. The residue yielded 0·14 g of lactone and 0·09 g of acid. A solution of the peroxide (0·45 g) in carbon tetrachloride (20 c.c.) was boiled for 1 hr and yielded 0·11 g of lactone and 0·07 g of acid.

(*b*) *3′-Nitrodiphenyl-2 carboxylic acid* was likewise converted into the *peroxide*,

which was recrystallised from aqueous acetone in needles, m.p. 123° (explosion) (Found N, 5·4. $C_{26}H_{16}O_8N_2$ requires N, 5·8%). Decomposition of this peroxide (0·29 g) in acetic acid gave 0·07 g of lactone, while decomposition of it (0·5 g) in carbon tetrachloride gave 0·15 g of lactone.

(*c*) *3′-Cyanodiphenyl-2 carboxylic acid* was treated with thionyl chloride and then sodium peroxide in the same fashion. A small amount of peroxide, m.p. 126° (explosion), separated but the majority, m.p. 118–120°, was recovered by evaporation of the solvent (toluene instead of *cyclo*hexane). Decomposition of the crude peroxide (0·5 g) in carbon tetrachloride furnished 0·1 g of lactone.

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Lactone of 2′-Hydroxy-5′-phenylazodiphenyl-2 Carboxylic Acid

Diazotised aniline (2·3 g) in dilute hydrochloric acid was added slowly with stirring to an ice-cooled solution of the lactone of 2′-hydroxydiphenyl-2 carboxylic acid (4·5 g) and sodium hydroxide (4·6 g) in water (25 c.c.). Acidification of the dark red solution yielded the *phenylazo-lactone* (6 g), which was recrystallised from ethanol in long orange needles, m.p. 174–175° (Found: C, 75·8; H, 4·0; N, 9·4. $C_{19}H_{12}O_2N_2$ requires C, 76·0; H, 4·0; N, 9·3%). This substance was soluble in boiling sodium hydroxide solution, but it was insoluble in sodium carbonate solution.

Coupling with three times as much diazonium salt gave a brown solid, which was soluble in both ether and sodium carbonate solution. Presumably this was 2′-hydroxy-3′:5′-bis(phenylazo)-diphenyl-2 carboxylic acid. As it could not be crystallised, it was reduced with sodium dithionite to an amino-compound, m.p. 235–240°, which yielded, with hot acetic anhydride and acetic acid, the *lactone* of *2′-hydroxy-3′:5′-bisacetamidodiphenyl-2 carboxylic acid*, having m.p. 350–353° after recrystallisation from acetic acid (Found: C, 65·5; H, 4·6; N, 8·9. $C_{17}H_{14}O_4N_2$ requires C, 65·8; H, 4·6; N, 9·0%).

Lactone of 2′-Hydroxy-5′-aminodiphenyl-2 Carboxylic Acid.

Sodium dithionite was added to a boiling aqueous solution of the 5′-phenylazo-lactone and sodium hydroxide until the red colour disappeared. The solution was cooled, washed with ether, heated, and acidified with sulphuric acid. Without delay it was poured into excess sodium carbonate solution. The *amino-lactone* which separated was recrystallised from ethanol and had m.p. 188–189° (Found: C, 73·7; H, 4·5; N, 6·6. $C_{13}H_9O_2N$ requires C, 73·9; H, 4·3; N, 6·6%). Its hydrochloride was scarcely soluble in water, but the sulphate was soluble in hot water.

Lactone of 2′-Hydroxy-5′-acetamidodiphenyl-2 Carboxylic Acid

The foregoing amino-lactone was acetylated with a hot mixture of equal parts of acetic anhydride and acetic acid. The 5′-acetamido-lactone was recrystallised from aqueous acetic acid and had m.p. 231–232° (Found: C, 70·9; H, 4·7; N, 5·6. $C_{15}H_{11}O_3N$ requires C, 71·1; H, 4·4; N, 5·5%).

Lactone of 2′-Hydroxy-5′-cyanodiphenyl-2 Carboxylic Acid

An attempt to prepare this compound from the amino-lactone by the Sandmeyer reaction failed. Recrystallisation of the material produced by decomposition of the peroxide gave *5′-cyano-lactone* with m.p. 203–204° (Found: C, 75·6; H, 3·1; N, 6·2. $C_{14}H_7O_2N$ requires C, 76·0; H, 3·2; N, 6·3%). The structure assigned to this substance rests purely on analogy with those of the other oxidation products.

Lactone of 2′-Hydroxy-5′-methoxydiphenyl-2 Carboxylic Acid.

The amino-lactone was diazotised by warming a suspension of its sulphate in dilute sulphuric acid with sodium nitrite. The solution was boiled during several hours and the light brown solid which separated was then methylated in chloroform solution with diazomethane. A small yield was obtained of the *5′-methoxy-lactone*, which was recrystallised from petroleum ether (b.p. 80–100°), m.p. 121–123° (Found: C, 74·6; H, 4·8. $C_{14}H_{10}O_3$ requires C, 74·3; H, 4·5%).

Lactone of 2′-Hydroxy-5′-nitrodiphenyl-2 Carboxylic Acid

The lactone of 2′-hydroxydiphenyl-2 carboxylic acid was warmed for 1 minute with excess concentrated nitric acid. The sparingly soluble *5′-nitro-lactone* separated and completely precipitated with water; it was recrystallised from acetic acid and had m.p. 259–261° (Found: C, 64·4; H, 3·0; N, 5·7. $C_{13}H_7O_4N$ requires C, 64·7; H, 2·9; N, 5·8%). Its structure was proved by reduction with tin and hydrochloric acid, followed by acetylation with acetic anhydride and acetic acid. The resulting 5′-acetamido-lactone had m.p. 230–232° undepressed by an authentic specimen. Previously[23] the nitration had been described as yielding a nitro-lactone with m.p. 224°.

Acknowledgement—We thank the Department of Scientific and Industrial Research for two maintenance grants.

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Tetrahedron, 1957, Vol. 1, p. 269. Pergamon Press Ltd., London

NOTE

Une méthode simple de synthèse du benzene $^{14}C_6$ et du styrolene $^{14}C_8$

(*Received* 30 *January* 1957)

Les méthodes publiées pour la synthèse due benzène ^{14}C ont été passées en revue par Turner et Warne.[1] Les mêmes auteurs[1] ont décrit une méthode élégante donnant un rendement global de l'ordre de 75% par rapport à $^{14}CO_2$ mis en oeuvre mais ce procédé comporte six étapes successives.

Nous avons donc examiné la possibilité d'utiliser la polymerisation cyclisante de l'acétylène en présence de "triphénylphosphine nickelcarbonyl:" $(C_6H_5)_3PNi(CO)_2$ comme catalyseur, selon Reppe[2] car, l'acétylène étant facilement préparé avec un rendement presque quantitatif[4] on devait pourvoir disposer d'une synthèse du benzène radioactif en deux étapes seulement à partir de $^{14}CO_3Ba$. Notons que ce procédé donne comme sous produit du styrolène uniformément marqué[2] également très intéressant. Bien qu'il soit fait mention,[3] sans aucun détail de l'application de la méthode de Reppe à l'échelle d'une molécule, il ne semble pas que l'on ait tenté jusqu'ici d'opérer sur des quantités de l'ordre de 10 millimoles d'acétylène.

Nous avons examiné les conditions pour obtenir un rendement optimum. Parmi les milieux réactionnels essayés: benzène, diméthylformamide, l'acétonitrile a donné les meilleurs résultats. Nous avons vérifié que la trimérisation de l'acétylène ne se produit pas à la pression atmosphérique mais pour une pression d'acétylène supérieure à 2 kg/cm^2. L'isolement du benzène du milieu réactionnel par l'intermédiaire du "clathrate" selon[1] ne nous a pas donné de résultats reproductibles, d'ailleurs ce procédé ne permet pas d'isoler facilement le styrolène. L'entrainement à la vapeur d'eau ou par un courant d'azote n'ayant pas donné de bons résultats, nous avons été amenés à utiliser comme moyen de séparation la chromatographie de partition en phase vapeur.

Succinctement, la technique à laquelle nous sommes arrivés après de nombreux essais est la suivante. Sur une rampe à vide, on condense 14,3 millimoles d'acétylène dans un tube de verre à parois épaisses (150 mm × 10 mm) renfermant 0,8 ml d'acétonitrile et 30 mg de catalyseur. Le tube scellé, placé dans un autoclave renfermant de la "carboglace" afin d'exercer une contre-pression, est chauffé à 80°C pendant 24 heures. Le mélange réactionnel est distillé sous vide et le distillat est introduit dans un appareil à chromatographie de partition en phase vapeur (colonne: l = 5 m 50, ϕ = 9 mm; support: "célite 545," phase Fixe: 30% de phthalate de nonyle; température: 75°C; éluant H_2: 16 ml/mn). Dans ces conditions, l'acétonitrile émerge de la colonne au bout de 45 minutes environ et le benzène 16 minutes environ après et l'élution du styrolène demande 18 heures. Ces diverses fractions sont condensées séparément dans un serpentin refroidi par l'azote liquide. On obtient 257 mg de benzène "chromatrographiquement" pur soit un rendement de 74% et récupère aussi environ 10% de styrolène pur.

On peut également effectuer la réaction dans un autoclave spécial de 12 ml. Pour les mêmes quantités de solvant et catalyseur que ci-dessus on peut introduire trois fois 12 millimoles d'acétylène. Les rendements obtenus sont comparables à ceux de la technique en tube scellé.

Le carbonate de baryum ^{14}C commercial a une activité spécifique de 18 mc/millimole, par le procédé décrit on pourrait donc préparer du benzène ayant une activité spécifique maxima d'environ 100 mc/millimole.

Une description plus détaillée sera faite ailleurs. De plus, nous poursuivons nos recherches sur la synthèse, selon ce principe, de composés benzéniques substitués, marqués dans le noyau.

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Tetrahedron, 1957, Vol. 1, pp. 270–271. Pergamon Press Ltd., London

PRELIMINARY COMMUNICATION

The direct introduction of the diazonium group into aromatic nuclei

(*Received* 2 *March* 1957)

THE conversion of an aromatic hydrocarbon into a diazonium salt, normally involves three steps, nitration, reduction to the amine, and diazotisation with nitrous acid. However, it has long been known that in certain instances it is possible to obtain diazonium salts directly from reactive aromatic compounds. The best known example is the formation of diazonium salts as by-products in the preparation of nitroso-phenols (quinone-monoximes). If phenols are treated with excess nitrous acid for long periods, the nitroso-derivatives first formed react further to yield diazonium salts.[1–4] Another reaction in which a diazonium group is directly introduced into aromatic nuclei, is the treatment of reactive aromatic compounds with a solution of nitrous acid in trifluoracetic anhydride.[5] The method only gives moderate yields of diazonium salt and very expensive trifluoroacetic anhydride is required.

It has now been shown that these two examples are special instances of a general reaction by which diazonium salts can be prepared directly from a variety of aromatic compounds by the action of nitroxyl derivatives of the type NO·X (X = Cl, HSO_4, ClO_4, CF_3COO, etc.). The reaction almost certainly involves the initial nitrosation of the aromatic nucleus followed by the conversion of the nitroso compound so formed into the diazonium salt.

$$ArH \xrightarrow[HX]{HNO_2} ArNO \xrightarrow[HX]{HNO_2} ArN_2^+X^-$$

The most reactive compounds, e.g. phenols, can be converted into diazonium salts in good yield by treating the aromatic compound in aqueous ethanol solution with hydrogen chloride and excess ethyl nitrite. By this method, phenol and *m*-cresol have been converted into the corresponding diazonium salts in 80 per cent and 45 per cent yields respectively. Tertiary amines can also be converted into diazonium salts by these reagents, small yields of the corresponding diazonium salts having been isolated from dimethyl and diethyl anilines. Polyalkyl benzenes and phenol ethers are converted into the corresponding diazonium salts by treating the aromatic compounds dissolved in nitrobenzene with nitrosyl sulphuric acid (either prepared separately from nitric acid and sulphur dioxide, or in situ by dissolving sodium nitrite in excess sulphuric acid before adding the nitrobenzene solution of the hydrocarbon). By this means diazonium salts have been prepared from anisole (48 per cent), mesitylene (78 per cent), and *m*-xylene (43 per cent). Low yields of diazonium salts have also been obtained from toluene and benzene by the direct reaction of solutions of sodium nitrite in sulphuric acid on the hydrocarbons. The diaxonium salts so obtained are the derivatives of nitrotoluene and nitrobenzene and not the simple hydrocarbons. Thus evidence for a general reaction by the following equation

$$ArH + 2HNO_2 \longrightarrow ArN_2^+ OH^- + H_2O + 2[O]$$

has been established. For certain compounds, namely phenols, phenol ethers and polyalkyl benzenes, the yields of diazonium salt obtained during the present exploratory work, are sufficiently large to suggest the reaction has considerable preparative value. However, the reaction appears likely to give

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only poor yields with toluene and benzene and does not take place at all with aromatic compounds containing deactivating groups. For such compounds considerable adaptation of the basic reaction is necessary in order to obtain significant yields of diazonium salt. Only one of several possible routes has so far been investigated.

In collaboration with G. Theaker a method for introducing a diazonium group directly into deactivated aromatic nuclei has been developed. The reaction involves the use of a mercury catalyst and is based on the earlier work of Bamberger,[6] and on the investigations of "Oxynitration" by Westheimer,[7] and Carmack.[8] The aromatic compound, dissolved in sulphuric acid, is treated with nitrosyl sulphuric acid (prepared in situ by the addition of sodium nitrite) and a catalytic amount of mercuric sulphate (1/100 mole). Using this method moderate yields of diazonium salt have been prepared from aromatic sulphonic acids [benzene sulphonic acid 20 per cent; *p*-toluene sulphonic acid 53 per cent], carboxylic acids [*p*-toluic acid 21 per cent; α-naphthoic acid 20 per cent] and aromatic nitro-compounds [*p*-nitro anisole 74 per cent; *p*-nitro toluene 37 per cent].

Full details of this work together with a discussion of the mechanism of the reactions will be submitted for publication shortly.

Acknowledgements—The author wishes to express his gratitude to Mr. G. Theaker (of I.C.I. Dyestuffs Division), who carried out the investigation of the mercury catalysed reaction. He also wishes to thank Prof. R. D. Haworth, F.R.S., for much encouragement.

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BOOK REVIEWS

J. ENGLISH and H. G. CASSIDY: **Principles of Organic Chemistry** (second edition). McGraw-Hill, New York, 1956. 473 pp. 49s.

THIS text book of 473 pages has been written to cover a first-year course in organic chemistry in such a way as to stress the fundamental principles of the subject. The reviewer believes that the authors have largely succeeded in their intentions. There are twenty-four chapters divided into sections, which are well indexed, so that it has been possible to use cross-references. The first chapter, or introduction, deals with the geometry of the carbon atom and the types of bond which it forms. Ions, radicals, formulae, and the various electronic effects are also defined. The hydrocarbons, acyclic and aromatic, are next described, followed by the chemistry of alcohols and phenols (described together), halogen compounds, ethers, carbonyl compounds, amines and derivatives, sulphur compounds, substituted acids including hydroxy, keto, and amino acids, brief reference to colour and chemical constitution, stereoisomerism, carbohydrates, macromolecules, and a chapter devoted to heterocyclic chemistry.

Each chapter ends with historical notes and a very useful summary; useful that is, if employed wisely. It is, unfortunately, only too common for students to try to exist on predigested information. A wide variety of exercises are also provided chapter by chapter and some answers are given.

In this book, organic chemistry has been approached from the underlying theory of reaction mechanism, treated qualitatively. Although there is a wide difference of opinion on the wisdom of this method of treatment, the reviewer is decidedly of the opinion that in a first-year course in organic chemistry the minimum of mathematics should be introduced: there are always many students who do not wish to pursue chemistry beyond one or two years.

There are a number of minor points in the treatment of the course of study which might be raised. Thus, whilst the authors quite rightly indicate how in a Friedel and Crafts reaction a carbonium ion is produced as the reacting entity, they omit to show how in, say, nitration the NO_2^+ ion is produced. The student could be left with the impression that sulphuric acid is employed merely for removal of water. Again, whilst it is shown that, in general, hydrolysis of carboxylic esters takes place by breakage of acyl-oxygen bond, it is not shown that alkyl esters of sulphonic acids undergo breakage of the oxygen-alkyl bond, a fact which is so important in alkylation reactions. There are other topics where a chance to impress a difference in behaviour of two somewhat similar series of compounds has been missed. But these are not serious criticisms.

The printing and the layout of the text is very good. There are a number of mistakes in formulae which will have to be corrected in a second edition.

The reviewer enjoyed reading this book and can commend it to students; he wonders whether the average student will pay 49s. for a text which will serve him for only one year.

W. COCKER

Organic Syntheses, Vol. 36. Editor in chief, N. J. Leonard. John Wiley & Sons, Inc., New York; Chapman & Hall, Ltd., London, 1956. 120 pp.

IT seems almost superfluous to be asked to review any volume of *Organic Syntheses*. These volumes, first published in 1921, and made into Collective volumes at ten-yearly intervals, are necessary literature of any chemical laboratory. The present volume (36; 1956) maintains the high standard of printing and general layout which is associated with this publication.

For convenience the compounds synthesised are arranged alphabetically although in the present volume this brings *cyclo*decanediol and *cyclo*decanone together early in the book and their precursor sebacoin or sebacil quite late. This review would be too lengthy if reference were made to all the compounds for which preparations are given, but it might not be out of place to mention that two methods for the preparation of ferrocene are given.

W. COCKER

S. T. YOFFE and A. N. NESMEYANOV: **A Handbook of Magnesium-Organic Compounds**, Pergamon Press, 1956. Vol. I, pp. 744; Vol. II, pp. 664; Vol. III, pp. 644. £24.

THIS ambitious work, by two distinguished Academicians, is a compilation of reactions involving the formation and the use of Grignard reagents and other organo-magnesium compounds. The first two volumes contain a list of 13395 reactions of substances—arranged in the order used in *Chemical Abstracts* indexes—with various Grignard reagents. This list (Section I) gives the products of the reactions and numerical references (5375, beginning with references to Russian authors in Cyrillic script and finishing with other references in Latin script). The third volume is essentially for cross-reference purposes and contains not only the literature references but also a formula index of end-products (Section II) of the reactions listed in the first two volumes, and a formula index of the Grignard reagents (Section III), excluding the simplest such as those derived from methyl, ethyl, phenyl, and tolyl halides. These formula indexes refer the reader to the number of the appropriate reaction to be found in the main list in the first two volumes. The three volumes are thus intended to be used together.

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The *Handbook*, with the exception of a few title pages, is a photo-lithographic reproduction of the Russian volumes. Since, however, the main list of reactions (Section I, the subject of the first two volumes) is described by means of conventional formulae in Latin script, its use does not require a knowledge of Russian. The extensive (330 page) index of end-products, which begins Volume III, is arranged in order of empirical formulae. This is also true of the 33 page index of Grignard reagents. Many compounds may be listed under one such formula, and these are described by Russian names. Even this index could be used without a knowledge of Russian since the numbers set against each name refer to the main list of reactions in which structural formulae are given in Latin script. However, a great deal of effort can be saved merely by transliteration of the Russian names into Latin script; this is very easily done and the transliterated names are usually recognisable without difficulty. The translator's preface, by Dr. A. L. Mackay, thoughtfully provides not only a table for the transliteration of Russian letters into their Latin equivalents, but also a glossary of some Russian chemical words whose meaning is not obvious after transliteration, and a few general hints on the use of the book for those who do not know Russian.

With the main volumes is provided a 31 page booklet comprising a Foreword by Professor W. Wardlaw, and translations of the Russian Preface and Introduction. The last contains the essential instructions on the use of the book and illustrations of the nomenclature adopted, including the linear representation of cyclic formulae. The Preface is mainly concerned with the contributions of Russian chemists to the study of Grignard reactions. Though there is reference to Barbier and Grignard, there is none to Gilman, or to Frankland, although organo-zinc compounds are discussed; however, the latter omission is rectified in the Foreword. Similarly, though the authors refer to Runge's excellent monograph, they do not mention the extremely useful recent (1954) and detailed 1384-page book by Kharasch and Reinmuth, *Grignard Reactions of Nonmetallic Substances*. It is probable that both works were prepared more or less at the same time, and they will certainly be compared. Kharasch and Reinmuth's book has the advantage of later literature coverage, up to *Chemical Abstracts* of June 1950, in spite of earlier publication, since the *Handbook* under review contains references published in abstract up to 1 January 1948; it has also the very great advantage of being a critical textbook in which yields are nearly always given, as well as a compilation of reactions. The *Handbook*, by contrast, has the advantage of including reactions of Grignard reagents with metallic as well as nonmetallic substances, and also the reactions of compounds in which magnesium is not directly linked to carbon. Both works aim to provide answers to similar kinds of enquiry about Grignard reagents and their use; Kharasch and Reinmuth's book differs essentially in being a critical text covering a narrower though still a remarkably wide range, and it must be pointed out that the *Handbook* costs over three and a half times as much.

Supplements are planned to keep the *Handbook* up to date. The organic compounds of magnesium will thus become one of the best documented of chemical topics. It is also most satisfactory to note the publication of the *Annotated Bibliography on the use of Organolithium Compounds in Organic Synthesis* with *Supplements*.

The reviewer has not read the *Handbook* page by page—not many chemists will—and has noticed no errors. A work of this kind is worth its high price only if the reader has confidence in its completeness. The *Handbook* is to be recommended, and nearly all chemical libraries should have a copy of this valuable contribution to an important subject.

G. E. COATES

R. P. LINSTEAD* and B. C. L. WEEDON:† **A Guide to Qualitative Organic Chemical Analysis.** Butterworths, London, and Academic Press, New York, 1956. xi + 169 pp. 21s. $4.50.

THE approach of the present text to the subject is slightly different from that commonly employed in most American universities. Instead of using the solubility of the compound as a starting point, the present authors turn instead to the type of procedure originally used by Mulliken and Huntress, in which the compound is initially classified according to its elemental analysis. The new system is otherwise rather different from the one of Mulliken and Huntress, however, as to the order in which functional groups are tested for.

The authors imply their general procedure is superior to others available, and state that it is sufficiently different to justify publication. That their procedure is different is apparent. The reviewer, however, while admitting to not actually having used their system in the laboratory, is not convinced that it is superior to the more commonly used ones as typified by those of Shriner and Fuson or McElvain. It would rather seem a matter of personal preference as to exactly how the various tests are conducted and their results interpreted.

The very small size of the book is a result of both rather fine printing, and of complete omission of any description of the techniques and apparatus used in manipulating small amounts of material. In regards to the latter, the authors comment that no printed directions can adequately replace practical demonstration.

The chemical tests used, besides the conventional ones, are good and up-to-date. The coverage of the less common compounds (e.g. azo, azoxy, nitroso, sulphonamides, thiomides, sulphonyl halides, etc.) is more detailed than usual while, as customary, highly specialized compounds (e.g. alkaloids, peptides, phosphorus derivatives, etc.) are not considered. Leading references are generally given where desirable.

The separation and identification of mixtures is exceedingly brief (four pages).

The use of spectra in deducing structure is not considered, and the reviewer regards this as unfortunate, since although it may tend to encourage an understanding of chemical methods of identification, it actually widens the gap between the subject as used in research and as taught in the course.

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Essays in Biochemistry. Edited by SAMUEL GRAFF, John Wiley and Sons, Inc., New York; Chapman and Hall Ltd., London, 1956. x + 345 pp. 52s.

IN this collection there are twenty-five essays written in honour of Hans Thacher Clarke on his retirement as Professor and Chairman of the Department of Biochemistry, College of Physicians and Surgeons, Columbia University, New York. The authors, all former students or academic associates of Professor Clarke, were given a completely free hand by the editor, both in regard to the subject and to the style of their contribution. This absence of editorial restraint, so seldom allowed to scientific authors, has resulted in a number of most interesting essays, several of which are excitingly speculative.

For those whose interest is in the chemistry of natural products there are the essays on "Some Metabolic Products of Basidiomycetes" by Dr. Marjorie Anchel and on "The Veratrum Alkamines" by Dr. Oskar Wintersteiner. Dr. William H. Stein gives an excellent account of the work on the determination of the amino-acid sequence in the protein ribonuclease, to which he and his colleagues at the Rockefeller Institute for Medical Research have made such a great contribution. The elucidation of the exact chemical structure of proteins, by methods which were exploited so brilliantly by Sanger with insulin, may lead a wider group of organic chemists to interest themselves in these macromolecules which, up to now, may have appeared to be rather too indeterminate and "messy" for serious consideration.

For the theoretical organic chemist there are the essays on "Tetrazoles as Carboxylic Acid Analogs" by Professor Robert M. Herbst and "The Structural Basis for the Differentiation of Identical Groups in Asymmetric Reactions" by Dr. Hans Hirschmann. In this last essay the author proposes a new criterion to decide whether, in a given case, two identical groups in a reactant can or cannot be differentiated from each other in any reaction. The author's ideas, and those of others, are discussed in detail and are illustrated by a number of examples.

Professor Erwin Chargaff in his provocative essay entitled "The Very Big and the Very Small: Remarks on Conjugated Proteins" enjoins future generations of investigators to continue to be astonished by the complexities of living organisms, to continue their probing to attain a deeper understanding of the chemical processes of cells and to beware of the too facile model experiment. Professor David Rittenberg, writing "On the Bigness of Enzymes" puts forward an hypothesis for the mechanism of action of oxidoreduction and hydrolytic enzymes. This hypothesis uses an analogy between enzymes and metal catalysts of the transition groups with vacant *d* orbitals which may be used for chemisorption. It is postulated that the electrons of the enzyme protein molecule could move in a periodic field arising from the regular linear arrangement of the peptide bonds of the polypeptide chain. The electrons in this excited state would be distributed in a number of discrete levels forming an energy band, the lower edge of which approaches closely to the ground state. Should a peptide substrate, say, approach the enzyme two of the π electrons of the carbonyl group might be transferred to a low level of the excited state energy band of the enzyme. The approach of a water molecule or an hydroxyl ion to the now positively charged substrate carbon atom is thus facilitated. The presence of divalent metal ions, which is often required for such enzyme reactions, would provide a set of energy levels which would facilitate the transfer of electrons to the enzyme.

There are other essays dealing with the biosynthesis of branched-chain compounds (Konrad Bloch), the biosynthesis of porphyrins (David Shemin), glycogen turnover (De Witt and Marjorie Stetten) and the biochemistry of the steroid hormones (L. L. Engel). Dr. Sarah Ratner gives a stimulating account of nitrogen transfer in biosynthetic mechanisms, in which the energy relations of the synthesis of urea are discussed. There are some thoughtful contributions on the more peripheral fields of biochemistry: lysogeny (Ernest Borek), unbalanced growth and death (S. S. Cohen), bacterial viruses (E. A. Evans), and the nature of cancer (Samuel Graff).

It is only natural that such a collection of essays should not all be of the same high level as some of those mentioned above, nor would one expect many to read straight through this book. There is no doubt, however, that every biochemist will find a great deal to interest him here, as will most organic chemists.

S. P. Datta

BOOKS RECEIVED

MIGRDICHIAN, VARTCES: *Organic Synthesis Vols.* I and II. 1882 pages (Reinhold Publishing Corporation, New York; Chapman and Hall Ltd., London, 1957) £14

KELLEY, L: *Organic Chemistry* (second edition) 757 pages. (McGraw-Hill Book Co. Ltd., 1957) $7.50 (56s. 6d.)

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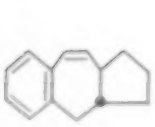
ERRATUM

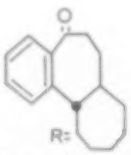
Tetrahedron **1/2,** 9 (1957): Alicyclic studies—XI. Attempted syntheses of 5:6-benzazulene and benzheptalenes.

The formula on p. 11 should read as follows:



XI

XII



XIII (a) R = H_2
(b) R = O

Tetrahedron, 1957, Vol. 1, pp. 277–283. Pergamon Press Ltd., London

REMARQUES SUR LA NOMENCLATURE DES TRITERPÈNES

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(*Received* 10 *July* 1957)

Résumé—On expose, pour faciliter leur discussion, certaines des règles de Nomenclature adoptées pour une Table de Pouvoir Rotatoire des Triterpènes, en préparation. Le nombre des squelettes fondamentaux a été réduit, et des préfixes nouveaux ont été introduits pour nommer des squelettes transposés.

Summary—The new, and drastically altered rules of nomenclature adopted for the preparation of a Table of Optical Rotations of Triterpenes are described in order to provide a larger basis for their discussion. The number of basic names has been reduced: only Lanostane, Ambrane, Onocerane, Oleanane, Ursane, Gammacerane and Lupane are used, each with precise stereochemical implications; such names as Tirucallane, Friedelane, etc. are considered as representing *modified* structures, and are not used. New prefixes are used to name these modifications of basic skeletons (in particular: *neo-* for the novic acid type of transposed skeletons, *friedo-* for the friedeline type of structure). The new rules should make it possible to name, without introducing new basic structures, many biogenetically possible but yet unknown Triterpenes.

LA PRÉPARATION d'une Table de Pouvoir Rotatoire des Triterpènes, dans le cadre des Tables de Constantes de l'Union Internationale de Chimie, a nécessité la dénomination systématique d'un grand nombre de corps. En l'absence de règles de Nomenclature adoptées par les instances internationales, il a été le plus souvent possible d'utiliser des propositions partielles, faites antérieurement par divers auteurs, et d'adapter les règles de Nomenclature des Stéroïdes.[1,2]

Toutefois, comme cela avait été le cas pour la Table de Pouvoir Rotatoire consacrée aux Stéroïdes,[2] des difficultés se sont présentées pour nommer certains groupes de Triterpènes et la Rédaction a dû préciser certaines règles ou en introduire de nouvelles. Dans quelques cas, la nécessité d'utiliser des règles aussi générales que possible, et de nommer *tous* les corps mentionnés, a conduit à modifier des conventions antérieures pourtant fort utiles, mais difficilement généralisables. Ces diverses innovations ont fait l'objet de consultations personnelles avec quelques Spécialistes, et nous avons pu dans une large mesure tenir compte de leurs suggestions et de leurs critiques. Si un accord complet n'a pas été obtenu sur tous les points, il a été généralement reconnu que les règles établies pour les Tables de Constantes pouvaient servir de point de départ à une Nomenclature définitive. Nous exposerons ici une partie des règles adoptées dans les Tables de Pouvoir rotatoire des Triterpènes, celles relatives aux squelettes fondamentaux et à leurs modifications. Nous espérons que cette note

* Les propositions faites ici engagent uniquement la responsabilité personnelle des Auteurs, et ne doivent pas être considérées comme bénéficiant de l'appui de l'U.I.C.P.A.

[1] A. Petit *Bull. Soc. Chim. Fr.* **16**, D545 (1949); *Bull. Soc. Chim. Fr.* **18**, numéro Mars–Avril (propositions de la Fondation Ciba) (1951); *Elsevier's Encyclopaedia of Organic Chemistry* Vol. 14, Supplément, p. 1347s–1367s Amsterdam (1954).

[2] J. P. Mathieu et A. Petit *Pouvoir Rotatoire Naturel* Vol. 1. Stéroïdes, p. 1f–9f et 1a–9a. Masson, Paris (1956).

permettra la discussion et facilitera le travail de la Commission de Nomenclature de l'U.I.C.P.A.

NOMS FONDAMENTAUX

Quelques structures fondamentales ont été choisies comme support de nomenclature, et sont traitées comme des hydrocarbures saturés.* La stéréochimie complète de ces structures fondamentales est définie comme il est indiqué plus loin, et est considérée comme impliquée dans la nomenclature, à l'exception des modifications effectivement explicitées avant le nom du squelette. Les structures fondamentales choisies sont les suivantes:

Groupe du Lanostane et groupes apparentés

Un seul squelette de base est utilisé: le *lanostane*, synonyme de 4,4,14α-triméthyl-(5α)cholestane dont la numérotation est conservée jusqu'en 27:

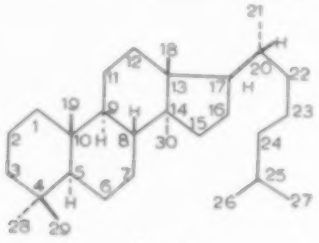

FIG. 1.

(Dans tous les Triterpènes, ce sont les méthyles α qui, dans les groupes *gem*-diméthyles, portent les numéros les moins élevés.)

Les dérivés des *groupes apparentés* au Lanostane portent des noms en "lanostane" complétés selon les modifications structurales:

(13α, 14β, 17βH)lanostane pour le groupe de l'Euphol

(13α, 14β, 17βH, 20αH)lanostane pour le groupe du Tirucallol

8β-méthyl-18-*nor*-lanostane pour les groupes de l'*iso*-Euphol et du Dammarane.

Exemples

Lanostérol 3β-hydroxy lanosta-8,24-diène.

Euphol 3β-hydroxy (13α, 14β, 17βH)lanosta-8,24-diène.

iso-Tirucallénol 3β-hydroxy 8β-méthyl-18-*nor*-(20αH)lanosta-13(17)-ène.

La *dégradation* de la chaîne en C_{17} est indiquée par *nor*- éventuellement précédé d'un préfixe multiplicateur.

Exemple

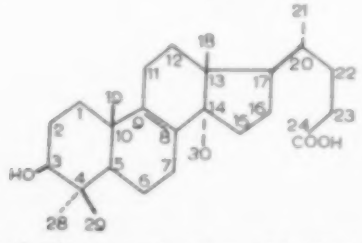

FIG. 2. 3β-hydroxy trinor-lanosta-8-ène 24-oïque

* Les noms fondamentaux ne désignent ainsi pas nécessairement des hydrocarbures saturés effectivement obtenus, mais sont *uniquement* un support de nomenclature.

Autres groupes

Les squelettes de base sont:

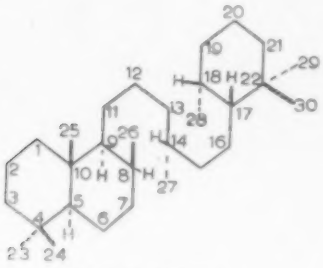

FIG. 3. Ambrane

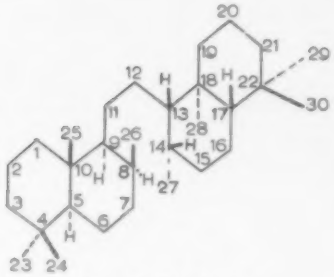

FIG. 4. Onocérane

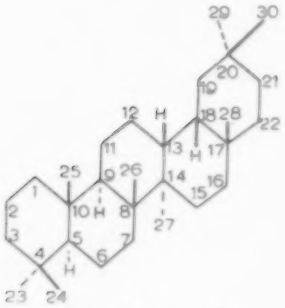

FIG. 5. Oléanane

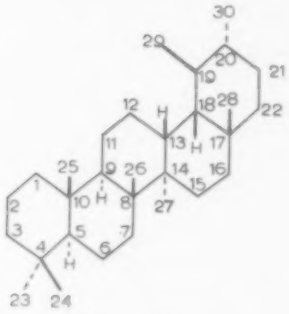

FIG. 6. Ursane

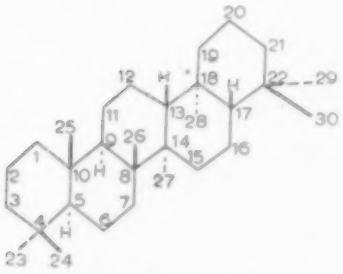

FIG. 7. Gammacérane

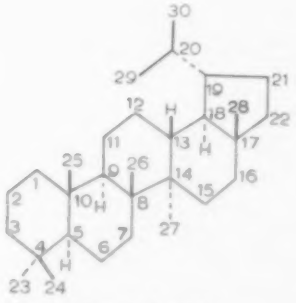

FIG. 8. Lupane

Exemples

Ambréine 8α-hydroxy ambra-13,18(28)-diène
α-Onocérine 3β,21α-dihydroxy onocéra-8(26),14(27)-diène
β-Amyrine 3β-hydroxy oléana-12-ène
α-Amyrine 3β-hydroxy ursa-12-ène
Taraxastérol 3β-hydroxy (18α, 19βH)ursa-20(30)-ène
Lupéol 3β-hydroxy lupa-20(30)-ène

MODIFICATIONS DE SQUELETTE

Des modifications des squelettes fondamentaux peuvent se rencontrer dans tous les groupes de Triterpènes. Elles sont commodément désignées par des préfixes accompagnant le nom fondamental.

Modifications du nombre de groupes méthyles

Le remplacement d'un groupe méthyle par un atome d'hydrogène est indiqué par le préfixe *nor-* précédé du numéro du (CH_3) ainsi supprimé. La configuration au centre asymétrique correspondant est conservée, sauf indication spéciale dans la configuration du squelette.

Modifications aux dimensions des cycles

La contraction d'un cycle avec élimination d'un atome de carbone est désignée par *nor-* précédé de la lettre caractéristique du cycle modifié et, entre parenthèses, du numéro de l'atome de carbone considéré comme éliminé. Cet atome est en principe celui dont le numéro est le plus élevé, à l'exception des atomes communs à deux cycles; si ce choix conduit à la perte de substituants en fait conservés dans le squelette modifié, on choisit comme atome disparu celui qui porte le numéro le plus faible.

Exemples

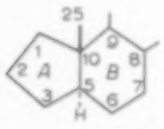

FIG. 9. 23,24-di*nor*-A(4)-*nor*-

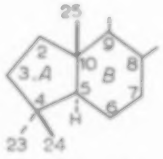

FIG. 10. A(1)-*nor*-

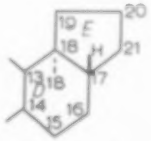

FIG. 11. 29,30-di*nor*-E(22)-*nor*-(série de l'Onocérane)

Modifications de squelette par transpositions

Deux types principaux de produits transposés sont décrits, soit comme produits naturels, soit comme dérivés d'élaboration des différents squelettes: les produits du type Acide novique (série *néo*), et les produits du type Friedeline (série *friedo*).

Série néo. Une série de transpositions conduit successivement, par contraction du cycle A puis migration des méthyles angulaires situés en 10 (jonction A/B), 8 (jonction B/C) et 14 (jonction C/D), aux squelettes partiels dont les modifications correspondantes sont désignées par A-*néo*-, A:B-*néo*-, A:C-*néo*- (pas d'exemple décrit jusqu'ici) et A:D-*néo*-, suivi du nom fondamental du squelette initial. On conserve le numérotage initial du squelette et des groupes méthyles ayant migré.

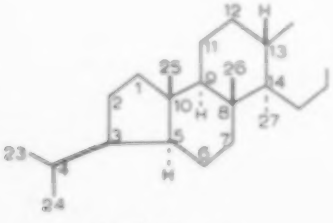

FIG. 12. A-*néo*-

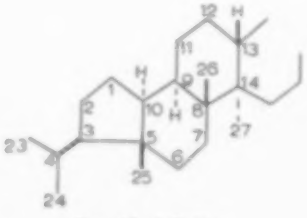

FIG. 13. A:B-*néo*-

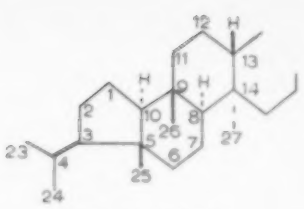

FIG. 14. A:C-*néo*-

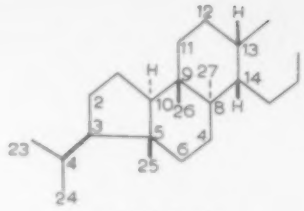

FIG. 15. A:D-*néo*-

Exemples

d-α-Amyratriène A-*néo*-ursa-3,9(11),12-triène

β-Amyrilène I A-*néo*-oléana-3,12-diène

Acide novique A:B-*néo*-(3ξ)ursa-12-ène 28-oïque 27:9α-olide

1-α-Amyradiène A:D-*néo*-(3ξ)ursa-12,14-diène

Série friedo. Ces produits dérivent des squelettes normaux par migration (expérimentale ou postulée) des groupes méthyles angulaires de 14 (jonction C/D) en 13, de 8 (jonction B/C) en 14, de 10 (jonction A/B) en 9, et de 4 (groupe axial 24, cycle A) en 5. Ceci conduit successivement aux modifications de squelette désignées par D-*friedo*-, D:C-*friedo*-, D:B-*friedo*- et D:A-*friedo*-, suivi du nom fondamental du squelette initial. On conserve le numérotage pour les cycles et pour les groupes méthyles.

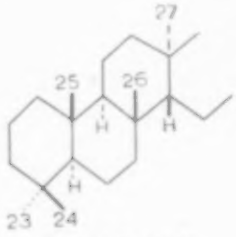

FIG. 16. D-*friedo*-

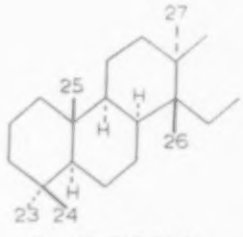

FIG. 17. D:C-*friedo*-

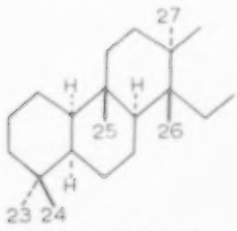

FIG. 18. D:B-*friedo*-

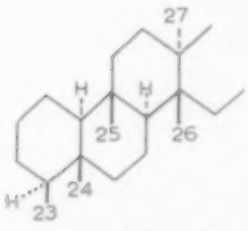

FIG. 19. D:A-*friedo*-

Exemples

Taraxérol 3β-hydroxy D-*friedo*-oléana-14-ène

Friedeline 3-oxo D:A-*friedo*-oléanane

Skimmilène I A-néo-D-*friedo*-oléana-3,14-diène

Remarques

(a) La nomenclature en *néo* ou *friedo* doit permettre de nommer sans difficulté des squelettes non encore décrits, mais certainement vraisemblables, au besoin en utilisant des termes tels que B-*néo*- (méthyle migré C-10 en C-5), E-*néo*- (méthyle migré de C-17 en C-18), etc.

(b) La nomenclature proposée suit de près des considérations biogénétiques. Malgré cet avantage, nous ne l'utilisons pas en série tétracyclique: elle conduirait alors à utiliser" Dammarane" comme squelette de base, et à considérer l'Euphane comme D-*friedo*-dammarane, mais à conserver le squelette du Lanostane, d'origine biogénétique différente. Ceci ne semble pas avantageux.

Modifications de squelette par suppression d'un cycle

L'élimination d'un cycle terminal et de tous ses substituants non angulaires est indiquée par *des-* suivi de la lettre caractérisant le cycle. La numérotation initiale est conservée.

Exemples

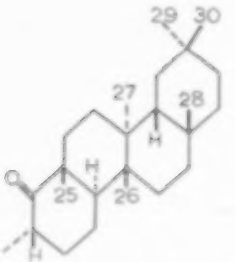

FIG. 20. 10-oxo *des*-A-D:A-*friedo*-(5βH)oléanane

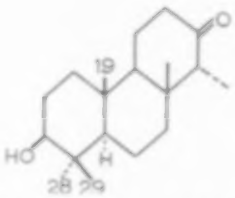

FIG. 21. 3β-hydroxy 13-oxo 8β-méthyl-18-*nor*-*des*-D-(14ξ)lanostane

Modifications de squelette par coupure d'un cycle

La coupure d'un cycle est indiquée par *seco-* précédé desnumèros des atomes entre lesquels a lieu la coupure. La numérotation est conservée. Si un ou plusieurs atomes de carbone sont en outre éliminés, on utilise les règles en *nor-* à partir du nom de base.

Exemples

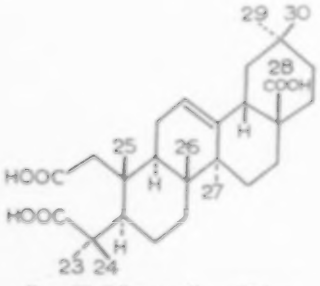

FIG. 22. 2:3-*seco*-oléana-12-ène 2,3,28-trioïque

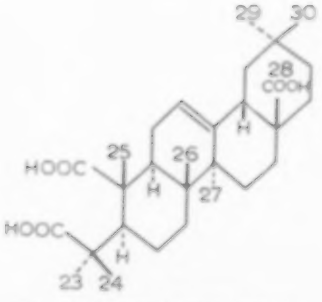

FIG. 23. 1:3-*seco*-2-*nor*-oléana-12-ène 1,3,28-trioïque

Modifications de squelette par cyclisation supplémentaire

On indique les cyclisations entre atomes du squelette de base par *cyclo-*. S'il en résulte une modification de la stéréochimie du squelette de base, elle est indiquée.

Exemples

cyclo-Arténol: 3β-hydroxy 9:19-*cyclo*-(9β)lanosta-24-ène

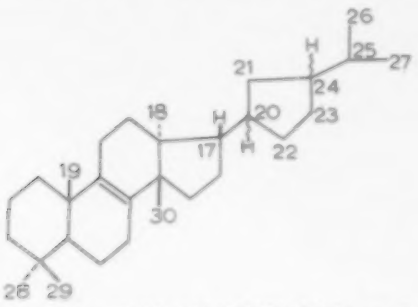

FIG. 24. 21:24-*cyclo*-(13α,14β,17βH,20ξ,24ξ)lanosta-8-ène

Nous remercions pour leurs suggestions et leurs critiques, MM. D. H. R. Barton, M.-M. Janot, O. Jeger, W. Klyne, E. Lederer, A. Petit et F. S. Spring.

Pour les propositions antérieures, on consultera notamment:

L. Ruzicka, F. C. Van der Sluys-Veer et O. Jeger *Helv. Chim. Acta* **26**, 280, 285 (1943).

D. H. R. Barton et C. W. Brooks *J. Chem. Soc.* 257, 261 (Note), (1951).

T. G. Halsall, E. R. H. Jones et G. D. Meakins *J. Chem. Soc.* 2862 (1952).

E. Menard, H. Wyler, A. Hiestand, D. Arigoni, O. Jeger et L. Ruzicka *Helv. Chim. Acta* **38**, 1517, (1955).

G. G. Allan, F. S. Spring, T. Stevenson et W. S. Strachan *J. Chem. Soc.* 3371 (1955).

Tetrahedron, 1957, Vol. 1, pp. 284–288. Pergamon Press Ltd., London

THE REACTION OF ALDEHYDES WITH 4-METHYL-4-PENTEN-2-OL AND α-TERPINEOL

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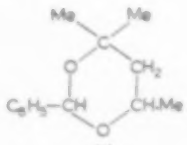
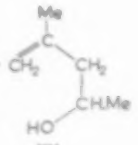
(*Received* 1 *August* 1957)

Abstract—The proton-catalysed interaction of aldehydes with 4-methyl-4-penten-2-ol affords a series of substituted tetrahydro-pyranols, which may be smoothly dehydrated to the corresponding dihydro-pyrans. The latter are converted by catalytic hydrogenation to tetrahydro-pyrans. α-Terpineol reacts analogously with, for example, benzaldehyde: the structure of the product so formed is discussed.

IN THE course of an attempted preparation of the virtually odourless cyclic acetal 4:4:6-trimethyl-2-phenyl-1:3-dioxan (I) by the action of hydrochloric acid on a mixture of benzaldehyde and 2-methyl-pentan-2:4-diol, under conditions rather more vigorous than those recommended in the literature,[1] a liquid by-product of similar volatility to that of the desired cyclic acetal was obtained. The by-product could not be effectively separated from the cyclic acetal by fractional distillation but it could be differentiated from it by gas chromatographic analysis and by virtue of its distinctive odour.

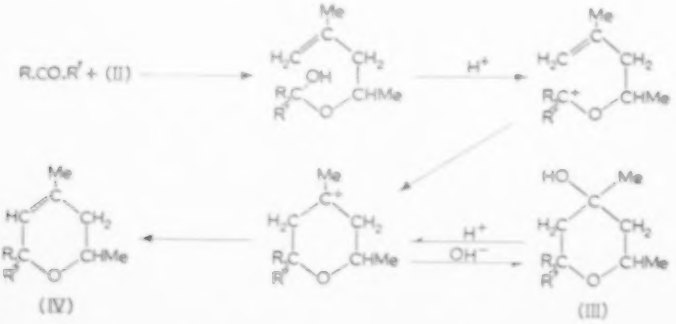


(I)



(II)

It was thought possible that an explanation of the formation of the odorous by-product might be found in the interaction of the primary dehydration product of 2-methyl-pentan-2:4-diol, viz: 4-methyl-4-penten-2-ol (II), with carbonyl compounds under the influence of acid catalysts. Substituted dehydro-pyrans are stated to result, according to the following reaction scheme:—[2]



[1] The cyclic acetal (I) is most conveniently prepared by the method of I. G. Farbenindustrie Brit. Pat. 346115.
[2] Williams *et al.* *J. Amer. Chem. Soc.* **72**, 5738 (1950); U.S. Pat. 2422648 and 2452977.

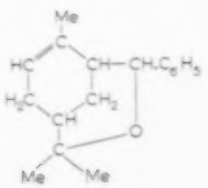
It was therefore assumed that in the original experiment 4-methyl-pentan-2:4-diol had to some extent decomposed under the influence of the anhydrous hydrochloric acid, affording (II) which had then reacted with the benzaldehyde. To confirm this hypothesis some of the reactions described by Williams *et al.*[2] were re-investigated and others were carried out with alternative aldehydes.

In contrast to the findings of Williams *et al.*, who did not report the isolation of 2:4-dimethyl-6-phenyl-tetrahydropyran-4-ol (III, R = C_6H_5, R′ = H), it was found that when benzaldehyde was condensed with (II) at 10–15° in the presence of one mole of sulphuric acid most (60–75 per cent) of the aldehyde reacted to give initially this pyranol. By distillation at a lower pressure than was employed by the previous workers (0·5 mm instead of 5 mm) it was isolated in a substantially pure form. This product could then be smoothly dehydrated by distillation from potassium bisulphate to yield 2:4-dimethyl-6-phenyl-3:6-dihydro-2(H)-pyran (IV, R = C_6H_5, R′ = H).

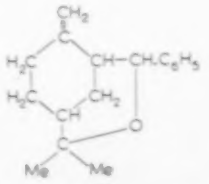
Other substituted pyranols and 2(H)-pyrans have been prepared analogously from anisaldehyde, cinnamaldehyde, piperonal, and heptaldehyde. The reaction product of (II) with citronellal afforded a mixture of four different products (gas chromatographic analysis) but these could not be effectively separated by distillation and were not further investigated. The possibilities of stereoisomerism which are latent in the pyranols were revealed in the case of the anisaldehyde reaction product (III, R = *p*-MeO·C_6H_4, R′ = H) by the isolation of two products having m.p. 126–127° and 84–86° respectively.

Catalytic hydrogenation of the 2(H)-pyrans proceeded smoothly, in the two cases investigated, to yield the corresponding tetrahydropyrans.

In view of the ease with which aldehydes were found to interact with (II) it was thought that α-terpineol might also react with aldehydes in a similar way, the structure of this compound favouring the steric requirements of the reaction. Interaction of benzaldehyde and α-terpineol under similar experimental conditions to those employed for (II) afforded a white solid, m.p. 64–65°. Analytical data suggested one of the structures (V) or (VI) by analogy with the reaction products of aldehydes with (II), but in this connection it is necessary to take into account the work of Lombard and Adam in this field.[3] These workers condensed benzaldehyde with *dl*-limonene under the influence of zinc chloride or sulphuric acid and obtained a compound, m.p. 62–63°. From *d*-limonene they obtained an analogous product, m.p. 93–95°. Repetition of the work of Lombard and Adam confirmed these results and a direct comparison of our compound, m.p. 64–65°, with theirs, m.p. 62–63°, became possible. Mixed melting point determinations and comparisons of infra-red spectra showed that they were identical.



(V)



(VI)

The French workers proposed three alternative formulae (all different from

[3] R. Lombard and J. Adam *Bull. Soc. Chim. Fr.* 1216 (1954).

(V) and (VI)) for their products. These were deduced by analogy with similar structures obtained by condensing limonene with formaldehyde, and were not supported by chemical evidence. Formulae (V) and (VI), unlike those of Lombard and Adam, meet our postulate of semi-acetal formation as the first stage of the reaction some reservation is, however, necessary at this stage as to the position of the double bond.

EXPERIMENTAL

4-Methyl-4-penten-2-ol (II). 2-Methyl-2:4-pentandiol (1770 g, 15 moles) was refluxed with anhydrous copper sulphate (0·9 g) until the boiling point fell to 80°. Slow distillation gave a fraction boiling below 100°, which was discarded, followed by a fraction b.p. 100–135° from which, by the addition of salt, the unsaturated alcohol was separated and redistilled, b.p. 72°/100 mm, through a Vigreux column. Yield: 834 g, i.e. 59 per cent overall, allowing for the recovery of 95 g of the original diol.

2(H)-*Pyrans* (IV). The general procedure recommended by Williams *et al.*[2] was followed. The aldehyde was added to the reaction mixture either at 10–15° or at such a rate that the temperature remained just below 30° without any effect on the course of the reaction. The reaction mixtures were allowed to stand at atmospheric temperatures for 36–48 hr in order to secure maximum yields of 2(H)-pyrans. At this point, after dilution of the reaction mixture with an equal volume of benzene, washing with 5 per cent aqueous sodium carbonate and water, and evaporation of the solvent and unchanged 4-methyl-4-penten-2-ol, the residue was submitted to fractional distillation *in vauco*. When it was desired to isolate the pyranol (III) distillation was carried out at 0·1–1 mm: otherwise 0·5–1 per cent of potassium bisulphate was added at this stage and the distillation carried out at such a pressure that the 2(H)-pyran distilled at ca. 150°. Physical and analytical data for the compounds thus obtained are shown in Table 1:

TABLE 1. COMPOUNDS OF GENERAL FORMULA (IV), (R′ = H)

R	B.p. (°/mm)	Formula	Required %		Found %	
			C	H	C	H
$C_6H_5^-$	78·5/0·7	$C_{12}H_{16}O$	82·92	8·58	83·21	8·58
p-$MeOC_6H_4^-$	98/0·05	$C_{14}H_{18}O_2$	77·00	8·30	77·19	8·56
$C_6H_5CH{:}CH^-$	96/0·18	$C_{15}H_{18}O$	84·07	8·47	83·84	8·55
3:4-$CH_2O_2C_6H_3^-$	102/0·15	$C_{14}H_{16}O_3$	72·39	6·94	72·36	6·85
n-$C_6H_{13}^-$	116–117/16·5	$C_{18}H_{32}O$	79·53	12·32	78·18	12·09

In general it was not found easy to separate the 2(H)-pyrans completely from their associated precursors, the pyranols (III). This applied particularly to the 2(H)-pyran derived from heptaldehyde (IV, R = C_6H_{13}–, R′ = H). The presence of a weak hydroxyl band in the infra-red spectrum of this product, even after repeated fractionation, explained the slightly low per cent carbon figure found by analysis.

2:4-*Dimethyl*-6-*phenyl*-3:6-*dihydro*-2(H)-*pyran* (IV, R = C_6H_5, R′ = H). (a) Benzaldehyde (318 g, 3 moles) and 4-methyl-4-penten-2-ol (267 g, 3 moles) were interacted

according to the above general method. After removing unchanged reactants a residue (458 g) remained, and this was distilled in portions. Thus a 47 g portion on distillation over potassium hydrogen sulphate (0·5 g) at 20 mm pressure afforded 38 g of dehydrated product. Redistillation afforded an analytically pure product, b.p. 72°/0·2 mm. Dehydration of larger batches proved impracticable due to the formation of malodorous by-products.

(b) Benzaldehyde (106 g, 1 mole), 4-methyl-4-penten-2-ol (100 g, 1·12 moles) and Amberlite IR-120 resin (30 g) were stirred for 12 hr at 60°. The resin was separated by filtration and the filtrate was distilled over potassium hydrogen sulphate (2 g), yielding, after fractionation 49 g (67 per cent, after allowing for recovery of unchanged reactants) of the required product.

Pyranols (III). The pyranols were isolated from the distillation residues (see notes under "2(H)-pyrans" above) by distillation, without a dehydrating agent, at a sufficiently low pressure. Yields varied from 60–75 per cent, and details of the pyranols studied are set out in Table 2:

TABLE 2. COMPOUNDS OF GENERAL FORMULA (III), R′ = H

R	B.p. (°/mm)	M.p.(°)	Formula	Required %		Found %	
				C	H	C	H
$C_6H_5^-$	114/0·7	30	$C_{13}H_{18}O_2$	75·69	8·80	75·17	8·71
p-$MeOC_6H_4^-$(a)	155–160/2	124–125	$C_{14}H_{20}O_2$	71·15	8·53	71·97	9·08
p-$MeOC_6H_4^-$(b)	155–160/2	84–85	$C_{14}H_{20}O_2$	71·15	8·53	71·82	9·03

Isomers (a) and (b) were separated by fractional crystallization from light petroleum (b.p. 40–60°), the former being the less soluble. Analytical figures indicated that traces of the dehydration products were present in both of them.

Tetrahydro-pyrans. The appropriate dihydro-pyran (IV) (100 g) was dissolved in ethanol (100 ml) and hydrogenated at normal pressures in the presence of Raney nickel catalyst freshly prepared from 20 g of alloy. Details of the compounds obtained are given in Table 3.

TABLE 3. TETRAHYDRO-PYRANS DERIVED FROM 2(H)-PYRANS (IV)

R	B.p. (°/mm)	Formula	Required %		Found %	
			C	H	C	H
$C_6H_5^-$	56/0·1	$C_{13}H_{18}O$	82·06	9·54	82·38	9·53
p-$MeOC_6H_4^-$	89/0·1	$C_{14}H_{20}O_2$	76·32	9·15	76·11	9·29

Reaction product of α-terpineol and benzaldehyde. α-Terpineol (154 g, 1 mole) containing sulphuric acid (1 g) was gradually added, with stirring, to benzaldehyde (106 g, 1 mole) at room temperature. The mixture was then heated to 120° for 3 hr. After cooling, it was diluted with benzene (200 ml), and washed first with dilute

sodium carbonate solution and then with water. After evaporation of the solvent, distillation *in vacuo* afforded a product (110 g, b.p. 117–125°/0·3 mm) which solidified on cooling. After recrystallization from methanol it had m.p. 64–65° (Found: C, 83·69; H, 9·15. $C_{17}H_{22}O$ requires C, 84·28; H, 9·15 per cent).

The authors thank the directors of Unilever Limited for permission to publish the results of this work.

Tetrahedron, 1957, Vol. 1, pp. 289–300. Pergamon Press Ltd., London

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POLAROGRAPHISCHE STUDIE DER REAKTIONEN DES 2:3-DIMERCAPTOPROPANOLS (BAL) MIT SCHWERMETALLEN UND EINIGEN OXYDATIONSMITTELN

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Aus dem Polarographischen Institut der Tschechoslowakischen Akademie der Wissenschaften, Prag (Direktor: Prof. Dr. J. Heyrovský)
und dem Institut für Arbeitshygiene und -schutz, Prag
(Direktor: Prof. Dr. J. Teisinger)

(*Received* 10 *May* 1957)

Abstract—In solutions of 2:3-dimercaptopropanol an anodic polarographic wave, corresponding to the formation of an insoluble mercury-salt, was observed. Using this wave the reactions of 2:3-dimercaptopropanol with heavy metals and some oxidants were followed. Further anodic and cathodic polarographic waves formed were used for the identification of reaction products. Metals of the first analytical group form insoluble bidentate-chelate complexes, those of the arsenic-group soluble monodentate compounds. It was confirmed that after adding 2:3-dimercaptopropanol the metal-ions, bound to proteins, are set free. Most of the 2:3-dimercaptopropanol in a living body is inactivated by oxidation. Due to this fact it is necessary to use great doses of the 2:3-dimercaptopropanol in clinical treatments. Disulphide is formed in oxidation by H_2O_2 or cystine. Monothiolecompounds are also formed during the reaction with cystine. In solutions of *p*-benzoquinone no disulphide results. Both SH-groupings react by 1:4-addition with two molecules of quinone.

Zusammenfassung—Mit Hilfe der polarographischen anodischen Stufe des 2:3-Dimercaptopropanols, welche einer Quecksilbersalzbildung entspricht, sowie mit Hilfe weiterer anodischer und kathodischer Stufen der Produkte wurde die Reaktion des 2:3-Dimercaptopropanols mit Schwermetallen und verschiedenen Oxydationsmitteln studiert. Die Metalle der ersten analytischen Gruppe bilden unlösliche Bidentat-Chelat-Komplexverbindungen, die der Arsengruppe lösliche Monodentatverbindungen. Die Lockerung der Metalle aus der Bindung an Eiweissstoffe durch Zugabe von 2:3-Dimercaptopropanol wurde bestätigt. Die Inaktivierung des grössten Teiles des 2:3-Dimercaptopropanols im Organismus wird durch Oxydationsreaktionen erklärt. Bei Oxydation durch Wasserstoffperoxyd oder Cystin entsteht ein Disulfid, bei der Behandlung mit *p*-Benzochinon geht—unter Teilnahme beider SH-Gruppen—eine 1:4-Addition vor sich.

DAS 2 : 3-Dimercaptopropanol (BAL), das anfangs gegen Vergiftungen durch Lewisit und andere organische Arsenverbindungen angewandt wurde, wurde später auch bei Intoxikationen durch andere Schwermetalle injiziert. Es wurde vorausgesetzt, dass BAL mit Metallen feste lösliche Komplexe bildet, welche die Auscheidung der

[1] R. A. Peters, L. A. Stocken und H. S. Thompson *Nature, Lond.* **156**, 616 (1945).
[2] L. L. Waters und Ch. Stock *Science* **102**, 601 (1945).
[3] S. Lewi *Pr. Méd.* **62**, 841 (1946).
[4] A. Gilman, F. S. Phillips, R. P. Allen, und E. S. Koelle *J. Pharmacol.* **87**, Suppl. 85 (1946).
[5] A. Gilman, R. P. Allen, F. S. Phillips, und E. St. John *J. Clin. Invest.* **25**, 549 (1946).
[6] E. S. G. Barron, Z. B. Hiller, und G. Kalnitsky *Biochem. J.* **41**, 62 (1947).
[7] L. A. Stocken *J. Chem. Soc.* 592 (1947).

Metalle aus dem Organismus ermöglichen. In einigen Fällen[1–10] wurde, vor allem auf Grund von Farbreaktionen[1,5,6,10,11,20] geschlossen, dass es zwischen den Metallen und dem Dimercaptopropanol zur Ausbildung von Komplexen kommt, welche sich durch eine Verfärbung und durch ihre Löslichkeit äussern, doch wurde ihre Existenz in der Mehrzahl der Fälle nicht nachgewiesen. Nur bei einigen wenigen Verbindungen, besonders beim Lewisit,[1–3,12,13,15] den Dichlorarsinen[7] und beim Oxophenarsin,[8] sowie weiter beim Quecksilber[5,15,19] und seinen Organoverbindungen,[17,18] wurde die Zusammensetzung der Komplexe vorgeschlagen oder bestimmt. Eine Studie der Reaktionen des 2 : 3-Dimercaptopropanols mit Quecksilber, Phenylquecksilber, Zink-, Kadmium-, Blei- und Silberacetat wurde in letzter Zeit konduktometrisch[21] durchgeführt. In dieser Arbeit wurde jedoch Pyridin als Lösungsmittel benützt, so dass die Bedingungen hier ziemlich weit von den physiologischen liegen.

R. Benesch und R. E. Benesch[18] untersuchten polarographisch die Komplexbildung organischer Quecksilberverbindungen (besonders von "Salyrgan" und Phenylquecksilber) mit Glutathion, einigen Peptiden und Dimercaptopropanol auf Grund der Reduktionsstufe des Komplexes, welche bei negativeren Potentialen als die Reduktionsstufe des an die Organoverbindung gebundenen Quecksilbers entsteht. Mit den anodischen Stufen befassten sich diese Verfasser nicht.

Das Ziel der vorliegenden Arbeit war, eingehendere Kenntnisse über die Zusammensetzung, das Verhalten und die Stabilität der Komplexe des 2 : 3-Dimercaptopropanols mit Schwermetallen zu gewinnen. Es wurde versucht, ob in dieser Weise die unterschiedliche Wirkung des Dimercaptopropanols bei Vergiftungen mit verschiedenen Schwermetallen nicht näher beleuchtet werden könnte. Dazu wurden die polarographischen anodischen Stufen des Dimercaptopropanols sowie die anodischen und kathodischen Stufen der entstehenden Komplexe untersucht. Weiter war es notwendig festzustellen, warum es den klinischen Erfahrungen gemäss notwendig ist, sehr hohe Tagesdosen der Ölsuspension des Dimercaptopropanols zu injizieren.

Um diese Fragen beantworten zu können war es notwendig:

(1) Das polarographische Verhalten des 2 : 3-Dimercaptopropanols zu studieren und die zweckmässigsten Bedingungen für das Studium der Reaktion aufzufinden.

(2) Den Einfluss der Metalle auf die Kurven des Dimercaptopropanols zu beobachten.

(3) Die Beeinflussung der Reaktion zwischen Dimercaptopropanol und Metallen durch die Anwesenheit von Eiweissstoffen zu studieren.

(4) Die Wirkung verschiedener Oxydationsmittel, welche in den Organismen vorliegen können (wie Sauerstoff, Peroxyde, Chinone und Disulfide), zu verfolgen.

[1] E. A. H. Friedheim und H. J. Vogel *Proc. Soc. Exp. Biol., N.Y.* **64**, 418 (1947).
[2] W. C. Kuzell, P. L. Pillsbury, und S. A. Gellert *Stand. Med. Bull.* **5**, 197 (1947).
[3] G. H. Spray *Biochem. J.* **41**, 360 (1947).
[5] N. D. Edge und G. F. Somers *Quart. J. Pharm.* **21**, 364 (1948).
[6] R. A. Peters *Proc. IX. Intern. Congr. Ind. Med.* S. 563 London (1948).
[7] L. A. Stocken und R. H. S. Thompson *Physiol. Rev.* **29**, 168 (1949).
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[10] M. L. Belenskij und V. J. Rozengart *Usp. Sovr. Biol.* **28**, 387 (1949).
[11] M. M. P. Paulssen *Acta Pharm. Intern.* **1**, 161 (1950).
[12] L. P. Barrack und R. A. Lehman *Science* **113**, 410 (1951).
[13] R. Benesch und R. E. Benesch *Arch. Biochem. Biophys.* **35**, 425 (1952).
[15] A. Mosig *Pharmazie* **8**, 403 (1953).
[20] R. Přibil und Z. Roubal *Chem. Listy.* **48**, 818 (1954).
[21] D. H. Rosenblatt und G. N. Jean *J. Phys. Chem.* **59**, 626 (1955).

EXPERIMENTELLER TEIL

Die polarographischen Kurven wurden mit den Polarographen des Systems Heyrovský, Erzeugung der Firma Zbrojovka n.p., Type V 301, in der üblichen polarographischen Schaltung und im Gefäss nach Kalousek mit getrennter Kalomelelektrode durchgeführt. Die verwendete Kapillare besass bei einer Quecksilberbehälterhöhe $h = 50$ cm eine Tropfzeit von $t = 3{,}4$ s und eine Durchflussgeschwindigkeit von $m = 1{,}90$ mg/s.

Das zur Verwendung gelangende 2 : 3-Dimercaptopropanol wurde von Dr. Ing. V. Hach (Forschungsinstitut für Pharmazie und Biochemie, Prag) hergestellt. Weiter wurde auch ein Präparat der Firma SPOFA verwendet.

Zur Herstellung der Puffer nach Britton und Robinson sowie des Acetat-, Citrat-, Phosphat-, Veronal- und Boratpuffers, des Puffergemisches Ammoniak-Ammoniumchlorid und der Natriumhydroxydlösung dienten Chemikalien vom Reinheitsgrad p.a. 0,01M Vorratslösungen der Metallsalze, verschiedener Oxydationsmittel und des Cysteins wurden von reinsten Chemikalien durch Auflösen in destilliertem Wasser vorbereitet. Die 0,01M Vorratslösung des 2 : 3-Dimercaptopropanols wurde täglich durch Auflösen der eingewogenen Menge in destilliertem Wasser oder in 20%-igem Äthanol frisch zubereitet, ebenso wie die äthanolische 0,01M Chinonlösung, welche im Dunkeln bei 0°C aufbewahrt wurde. 0,01M Cystinlösung wurde durch Auflösen des Präparats in 1M-NH_3 vorbereitet. Serumalbumin aus Pferdeblut wurde in destilliertem Wasser bei 20°C nach Anschwellen aufgelöst.

Die Mehrzahl der Versuche bei der Verfolgung der Komplexbildung der Schwermetalle mit 2 : 3-Dimercaptopropanol sowie der Oxydation dieser Verbindung wurde so durchgeführt, dass zu der sauerstoffbefreiten Pufferlösung, die das Dimercaptopropanol in einer Konzentration von 1×10^{-4}M bis 2×10^{-4} Menthielt, die Metallsalzlösung oder die Lösung des Oxydationsmittels allmählich zugegeben und nach jeder einzelnen Zugabe die polarographische Kurve aufgenommen wurde.

Da die erhaltenen Ergebnisse die Ausgangspunkte zur Feststellung der Beziehungen zwischen dem chemischen und pysiologischen Verhalten der einzelnen Komplexe sein sollten, wurden nicht zu weit vom pH-Wert 7 liegende Bedingungen gewählt. Mit Rücksicht auf die Unlöslichkeit der Phosphate der Schwermetalle konnten bei der Verfolgung der Komplexbildung die Phosphatpuffer nicht verwendet werden. Sofern die Bestandteile des Grundelektrolyten, z.B. Citrate oder Ammoniak, Komplexe mit den untersuchten Metallen bildeten, waren diese durchwegs wesentlich schwächer als die Komplexe mit dem Dimercaptopropanol und ihr Einfluss konnte in der Mehrzahl der Fälle vernachlässigt werden.

Bei Verfolgung der Oxydation der Lösungen des 2 : 3-Dimercaptopropanols durch Sauerstoff wurde das Gas in die Lösung aus einer Stahlflasche mit der Geschwindigkeit 50 ml/Min eingeleitet und nach Zeitintervallen wurden die Proben entnommen.

Bei der Verfolgung der Reaktion zwischen 2 : 3-Dimercaptopropanol und Cystin wurde der Einfluss der Cystinkonzentration in der Weise studiert, dass die Reaktiongemische, welche eine konstante Dimercaptopropanolmenge und verschiedene Cystinkonzentrationen enthielten, bis zur Beendigung der Reaktion (etwa 2 Stunden) in der inerten Stickstoffatmosphäre gehalten wurden. Nach dem Ablauf der Reaktion wurden die polarographischen Kurven registriert.

Die anodischen Stufen des 2:3-Dimercaptopropanols

Bei sehr kleinen Konzentrationen des Dimercaptopropanols wurde im gesamten pH-Bereich eine anodische[22,23] Stufe beobachtet (Abb. 1), welche der Bildung eines Komplexes mit dem Quecksilber zukommt. Die Stufe entspricht einem Zweielektronenvorgang. Aus dem Verhalten der anodischen Stufe[22] kann nicht entschieden

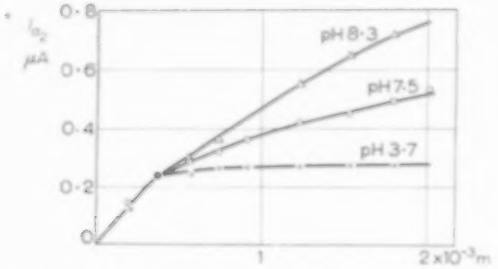
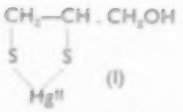
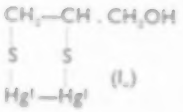


Abb. 3. Abhängigkeit des Stromes beim Potential der Adsorbatbildung (i_{a_2}) von der Konzentration des 2:3-Dimercaptopropanols bei verschiedenen pH-Werten.

werden, ob der entstehenden Verbindung die Formel (*I*) oder (*I$_a$*) zugeschrieben werden soll.



(I)



(I$_a$)

Aus dem Verhalten nach der Zugabe von Quecksilber(II)-verbindungen (S) kann mit Sicherheit geschlossen werden, das sich eine Quecksilberbindung bildet, die keine freie SH-Gruppe enthält.

Bei höheren Konzentrationen des Dimercaptopropanols wird die Stufe durch Adsorptionserscheinungen kompliziert (Abb. 2). Im ganzen pH-Bereich wurde eine negativere Adsorptionsvorstufe, bei pH $>$ 8 noch eine positivere Adsorptionsstufe beobachtet. Daneben wird die gesamte Stufe bei höheren Konzentrationen adsorptionsbedingt. Die Abhängigkeit der Stufenhöhe von der Konzentration bei verschiedenen pH-Werten ist aus Abb. 3 ersichtlich. Im mittleren pH-Bereich bildet sich das Adsorbat bei positiveren Potentialen als die Hauptstufe, so dass die Kurven die Form besitzen, die aus der Abb. 4 ersichtlich ist.

Aus den gewonnenen Erkenntnissen folgt, dass beim Studium der Reaktionen des 2:3-Dimercaptopropanols die Konzentration des Dithiols in der polarographierten Lösung höchstens 2×10^{-4}M sein darf. Unter solchen Bedingungen ist die Gesamthöhe der anodischen Stufe eine lineare Funktion der Konzentration des Dimercaptopropanols und die störenden Adsorptionseinflüsse machen sich nicht geltend.

Die anodische Stufe des 2:3-Dimercaptopropanols eignet sich auch zu analytischen Zwecken. Bei der Bestimmung z.B. in Injektionslösungen löst man die Ölsuspension in Chloroform und Äthanol und registriert die polarographische Kurve nach Vermischen mit dem Acetatpuffer vom pH 4,7.[24]

[22] P. Zuman, R. Zumanová und J. Teisinger *Chem. Listy.* **48,** 1499 (1954); *Collection* **20,** 139 (1955).
[23] C. Calzolari und A. Donda *Univ. Studi. Trieste, Fac. Sci. Ist. Chim.* No. 3, 16 (1954); *Chem. Abstr.* **49,** 7449 (1955).
[24] R. Zumanová und P. Zuman *Pharmazie* **9,** 554 (1954).

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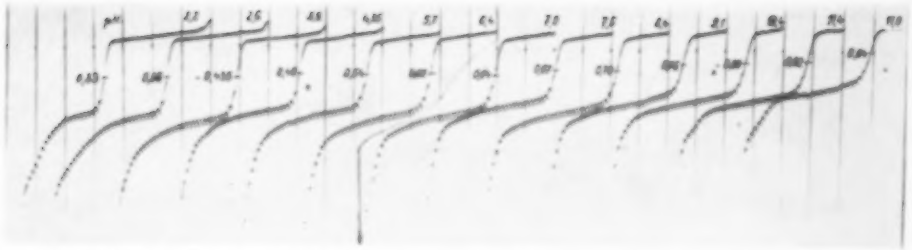


Abb. 1. pH-Abhängigkeit des 2:3-Dimercaptopropanols bei der Konzentration 9×10^{-5} M. Britton-Robinson-Pufferlösungen, pH-Werte am Polarogramm angegeben. Kurven von der 9. Drahtwindung zurück, anod.-kathod., SKE, 200 mV/Absz., $h = 50$ cm, Empf. 1:10.

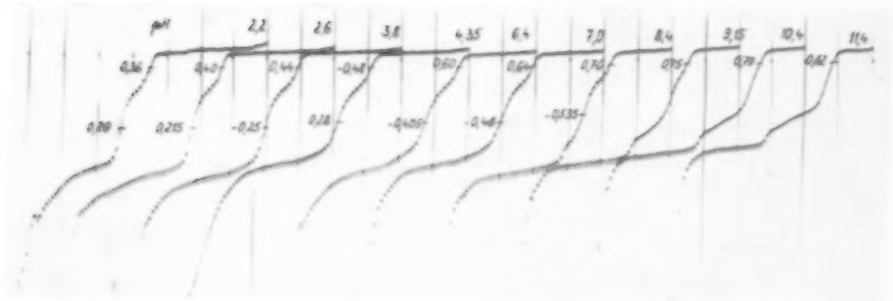


Abb. 2. pH-Abhängigkeit der Dimercaptopropanolstufe bei der Konzentration 3×10^{-5} M. Britton-Robinson-Pufferlösungen, pH-Werte am Polarogramm angegeben. Kurven von der 9. Drahtwindung zurück, anod.-kathod., SKE 200 mV/Absz., $h = 50$ cm, Empf. 1:30.

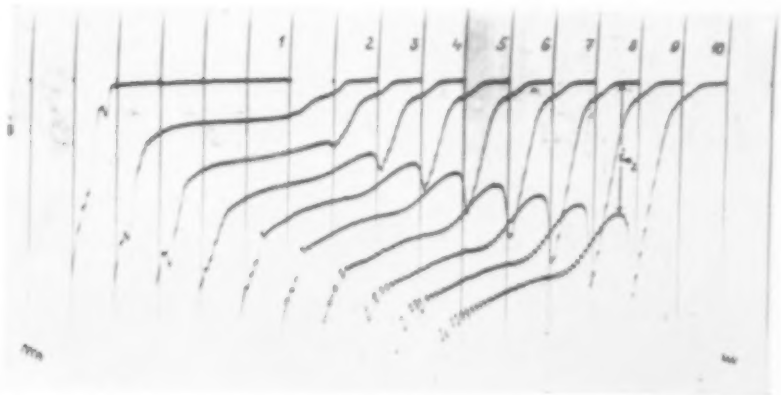


Abb. 4. Konzentrationsabhängigkeit der 2:3-Dimercaptopropanolstufen im Britton-Robinson-Puffer vom pH 7,5. Konzentration des Dimercaptopropanols: (1) 0; (2) 1,0; (3) 1,96; (4) 2,91; (5) 3,85; (6) 4,75; (7) 6,65; (8) 8,25; (9) 9,1; (10) 12,3 $\times 10^{-5}$ M. Kurven von der 8. Drahtwindung zurück, anod.-kathod., SKE, 200 mV/Absz., $h = 50$ cm, Empf. 1:70.

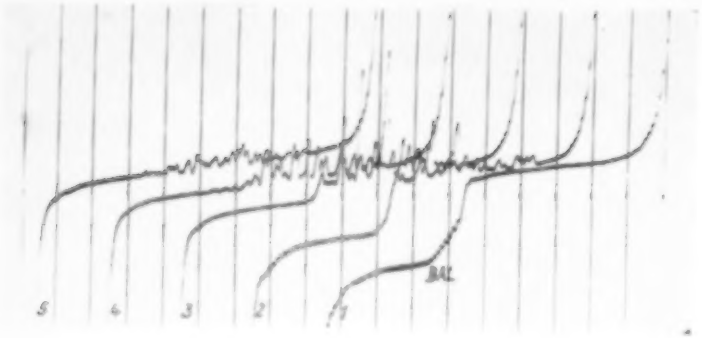


Abb. 5.
Komplex des Quecksilbers mit 2:3-Dimercaptopropanol. 5 ml Acetatpuffer vom pH 4,7 bis 1,97 × 10^{-4} M 2:3-Dimercaptopropanol.
Zugegeben (1) 0; (2) 0,59; (3) 1,16; (4) 1,74; (5) 3,2 × 10^{-4} M-Hg^{2+}. Kurven von der 12. Drahtwindung zurück aufgenommen, SKE, 200 mV/Absz., h = 50 cm, Empf. 1:20.

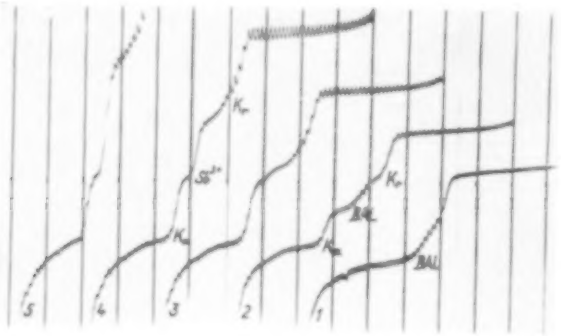


Abb. 6.
Komplex des Antimons mit 2:3-Dimercaptopropanol. 5 ml Veronalpuffer vom pH 7 mit 1,97 × 10^{-4} M 2:3-Dimercaptopropanol. Zugegeben: (1) 0; (2) 0,39; (3) 0,59; (4) 1,16; (5) 1,74 × 10^{-4} M-Sb^{3+}. Kurven von der 11. Drahtwindung zurück aufgenommen, SKE, 200 mV/Absz., anod.-kathod., h = 50 cm, Empf. 1:20.

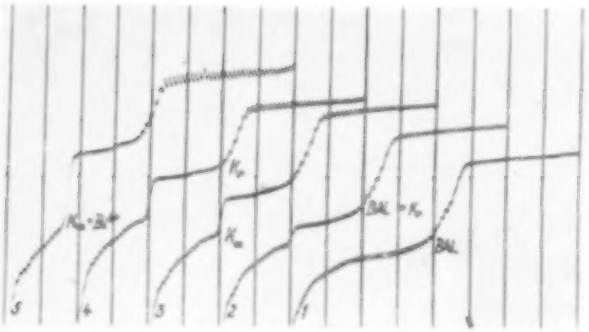


Abb. 7.
Komplex des Wismuts mit 2:3-Dimercaptopropanol. 5 ml Boratpuffer vom pH 8,6 mit 1,97 × 10^{-4} M 2:3-Dimercaptopropanol. Zugegeben: (1) 0; (2) 0,196; (3) 0,39; (4) 0,59; (5) 1,16 × 10^{-4} M-Bi^{3+}. Kurven von der 11. Drahtwindung zurück aufgenommen, SKE, 200 mV/Absz., anod.-kathod., h = 50 cm, Empf. 1:20.

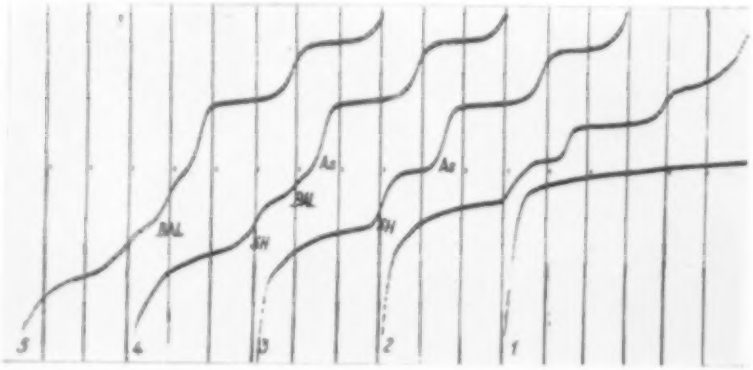


Abb. 8.
Komplex des Arsens mit 2:3-Dimercaptopropanol. 5 ml Citratpuffer vom pH 5,35 mit 9,4 × 10^{-4} M-As^{3+}. Zugegeben (1) 0; (2) 0,84; (3) 1,54; (4) 3,21; (5) 2,86 × 10^{-2} M 2:3-Dimercaptopropanol.
Kurven von der 14. Drahtwindung zurück aufgenommen, SKE, 200 mV/Absz., anod.-kathod., h = 50 cm, Empf. 1:100.

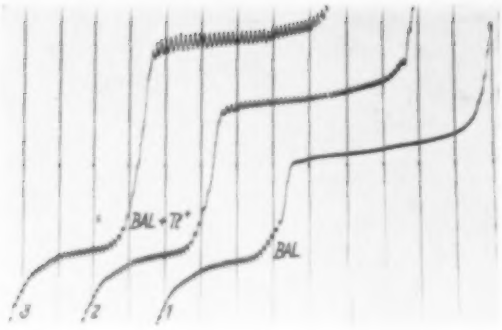


Abb. 9.
Kurven einer 2:3-Dimercaptopropanollösung in Gegenwart von Thallium. 5 ml Acetatpuffer vom pH 4,7 mit $1{,}97 \times 10^{-4}$ M 2:3-Dimercaptopropanol. Zugegeben: (1) 0; (2) 0,59; (3) $1{,}16 \times 10^{-4}$ M-Tl^+. Kurven von der 12. Drahtwindung zurück aufgenommen, SKE, 200 mV/Absz., $h = 50$ cm, Empf. 1:15.

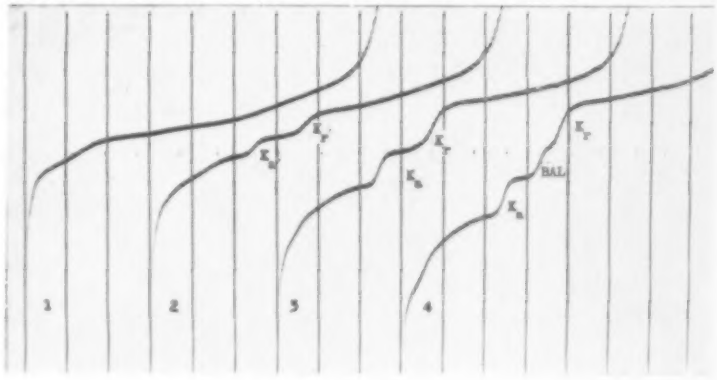


Abb. 10.
Einfluss des 2:3-Dimercaptopropanols auf Sb^{3+} in 2%iger Albuminlösung. 2% Albumin im Citratpuffer pH 5,8 mit 6×10^{-5} M-Sb^{3+}. Zugegeben: (1) 0; (2) 0,6; (3) 1,18; (4) $1{,}76 \times 10^{-4}$ M Dimercaptopropanol. Kurven von der 2. Drahtwindung aufgenommen, SKE, 200 mV/Absz., anod.-kathod., $h = 50$ cm, Empf. 1:20.

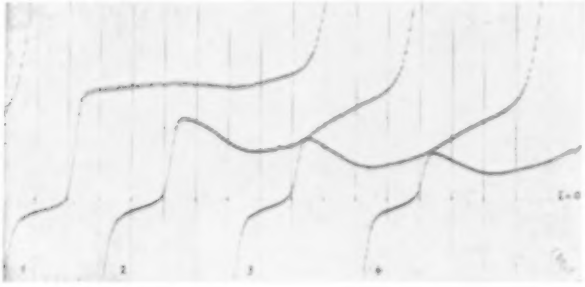


Abb. 11.
Einfluss des Albumins auf die Kupferstufe. Citratpuffer pH 6,1; $3{,}85 \times 10^{-4}$ M-Cu^{2+} Zugegeben: (1) 0; (2) 0,19%; (3) 0,81%; (4) 1,23% Albumin aus Pferdeblut. Kurven von der 2. Drahtwindung aufgenommen, SKE, 200 mV/Absz., anod.-kathod., $h = 50$ cm, Empf. 1:30.

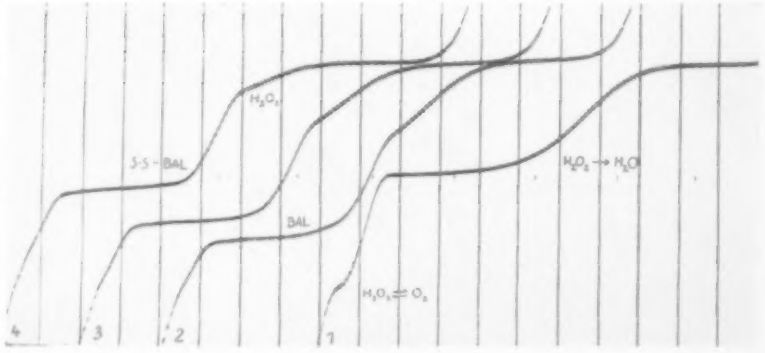


Abb. 12.
Reaktion des Dimercaptopropanols mit Hydroperoxyd. Zeitabhängigkeit der Disulfidbildung durch Hydroperoxyd-Oxydation des Dimercaptopropanols. Boratpuffer pH 9,3. (1) $2{,}94 \times 10^{-4}$-H_2O_2 allein; (2) $2{,}88 \times 10^{-4}$ M-H_2O_2 mit 2:3-Dimercaptopropanol gleich nach Vermischen; (3) nach 8 Minuten; (4) nach 45 Minuten. Kurven von der 14. Drahtwindung zurück aufgenommen, SKE, 200, mV/Absz., anod.-kathod., $h = 50$ cm. Empf. 1:20, $T = 20°C$.

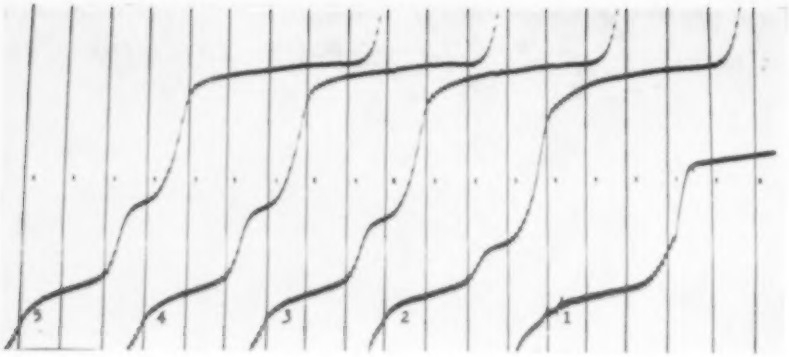


ABB. 13. Reaktion des Dimercaptopropanols mit Cystin. Zeitabhängigkeit der Reaktion bei dem Verhältnis Dimercaptopropanol:Cystin = 2:1. Phosphatpuffer pH 6,8. Kurve (1) $1{,}96 \times 10^{-4}$ M Dimercaptopropanol. Dazu wurde zugegeben $0{,}94 \times 10^{-4}$ M Cystin und die Kurven wurden (2) gleich; (3) nach 10 Minuten; (4) nach 20 Minuten; (5) nach 30 Minuten von der 14. Drahtwindung zurück registriert, SKE, 200 mV/Absz., anod.-kathod., h = 50 cm, Empf. 1:20.

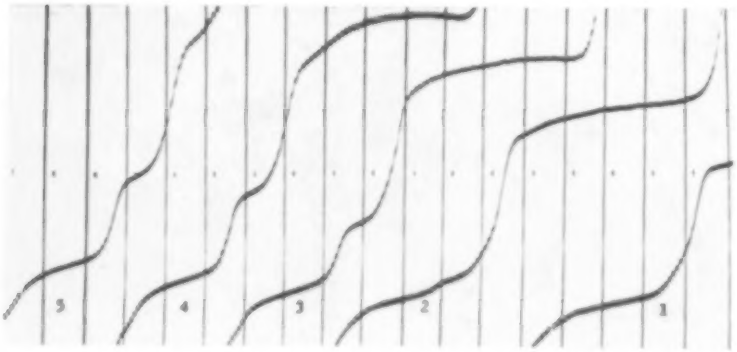


ABB. 14. Reaktion des Dimercaptopropanols mit Cystin. Abhängigkeit von der Cystinkonzentration. Phosphatpuffer pH 6,8 mit $1{,}96 \times 10^{-4}$ M Dimercaptopropanol. Cystinkonzentration: (1) 0; (2) 0,59; (3) 1,15; (4) 1,74; (5) $2{,}3 \times 10^{-4}$ M. Kurven von der 14. Drahtwindung nach 20 Minuten Stehens zurück aufgenommen, SKE, 200 mV/Absz., anod.-kathod., h = 50 cm, Empf. 1:20.

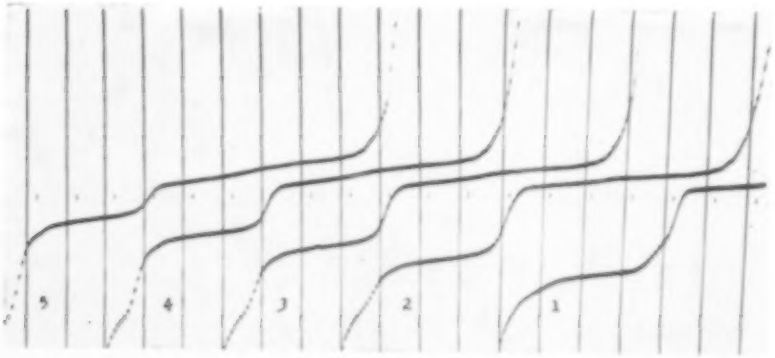


ABB. 15. Reaktion des Dimercaptopropanols mit Chinon. Phosphatpuffer pH 6,8 mit $1{,}96 \times 10^{-4}$ M Dimercaptopropanol. Chinonkonzentration: (1) 0; (2) 0,59; (3) 1,15; (4) 1,74; (5) $3{,}2 \times 10^{-4}$ M. Kurven von der 14. Drahtwindung zurück aufgenommen, SKE, 200 mV/Absz., anod.-kathod., h = 50 cm, Empf. 1:30.

Die Verbindungen der Schwermetalle mit dem 2:3-Dimercaptopropanol

Als so die Bedingungen der Reaktion sichergestellt wurden, wurde der Einfluss der Zugabe der Lösungen von 17 der häufigsten Schwermetalle auf die polarographischen Kurven der Dimercaptopropanollösungen studiert. Die einzelnen Stufen bei verschiedenen Konzentrationen der Metalle wurden verglichen.

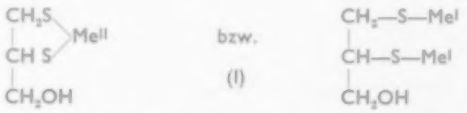
So war es möglich zu bestimmen, welche anodische Stufe (a) dem Rest des 2:3-Dimercaptopropanols und welche (b) den gebildeten Komplexverbindungen mit einer freien SH-Gruppe (Typus CH_2OH . $CHS(Me)CH_2SH$) entsprechen. Beide diese Stufen sind durch die Bildung eines Quecksilbersalzes limitiert bei 2:3-Dimercaptopropanol mit zwei SH-Gruppen, bei den Komplexverbindungen mit einer SH-Gruppe. Die Quecksilberverbindungen, welche an der Elektrodenoberfläche gebildet werden, sind bei Dithiolen fester als bei Monothiolen. Im Einklang damit liegen die Stufen der Monothiole bei positiveren Potentialwerten als diejenigen der Dithiole.

Einfacher war die Identifizierung der kathodischen Stufen. Wenn neben der Stufe des Überschusses des freien Metalls eine andere Reduktionsstufe beobachtet wurde, konnte diese Stufe der Reduktion des Metalls aus der Verbindung mit 2:3-Dimercaptopropanol zugeschrieben werden. Die Reduktion der Komplexverbindung verlief in allen Fällen (ähnlich wie es bei den von Benesch[18] studierten Beispielen der Fall war) bei negativeren Potentialen als diejenigen des freien Metalls.

Die Interpretation der polarographischen Kurven wurde dadurch erschwert, dass die anodische Stufe des 2:3-Dimercaptopropanols bei ziemlich negativen Potentialen liegt (etwa bei −0,8 V im untersuchten pH-Bereich). Dadurch war die Bildung von gemischten Strömen entweder mit der Reduktionsstufe des freien Metalls oder mit der Reduktionsstufe des Metalls aus der Komplexverbindung möglich. In solchen Fällen wurde z.B. die anodische Stufe des 2:3-Dimercaptopropanols (oder seiner Metallverbindung) über die Galvanometernullinie hinauf verschoben. Auch die Koinzidens der Halbstufenpotentiale einer der anodischen mit einer der kathodischen Stufen erschwerte die Indentifizierung der Stufen.

Nach ihrem polarographischen Verhalten konnten die studierten Metalle in einige Gruppen[25] eingeteilt werden. Die Einteilung ist ähnlich wie bei den analytischen Gruppen des Schwefelwasserstoffsystems, was in Anbetracht der Ähnlichkeit der Liganden begreiflich ist.

Au^{III}, Ag^{I}, Hg^{II}, Phenylquecksilber und Cu^{II} bilden in allen verwendeten Puffern Verbindungen vom Typus (I)



in welchen beide SH-Gruppen des Dimercaptopropanols durch das Metall besetzt sind und welche durchwegs wenig löslich sind. Auf den Polarogrammen beobachten wir nach Zugabe des Metalls eine Erniedrigung der anodischen Stufe des Dimercaptopropanols (Abb. 5). Die entstehende Verbindung bildet kolloidale Lösungen, so dass keine Reduktionsstufe des Metalls aus der Verbindung, sondern nur eine unregelmässige Depolarisation durch die kolloidalen Teilchen beobachtet wird

[25] Zuman P. und R. Zumanová *Chem. Listy.* **49**, 652 (1955); *Collection* **21**, 123 (1956).

(Abb. 5). Das Verhältnis des Metalls zum Dimercaptopropanol in der gebildeten Verbindung wurde durch polarometrische Titration bestätigt (Tabelle 1).

As^{III}, Sb^{III}, Bi^{III} bilden lösliche farbige Verbindungen vom Typus (II)

in welchem mit einem Mol des Metalls drei Mole des Dimercaptopropanols reagieren, wie aus der Abnahme der anodischen Stufe des Dimercaptopropanols mit Hilfe der polarometrischen Titration mit einer Metallsalzlösung festgestellt wurde.

Nach der Metallzugabe verkleinert sich in diesen Fällen die anodische Stufe des

TABELLE 1. BEOBACHTETE KURVENARTEN UND ZUSAMMENSETZUNG DER ENTSPRECHENDEN KOMPLEXE

Verhältnis Metall: 2:3-Dimercaptopropanol†					Metall	Komplextypus‡				
Puffer						Puffer				
Acetat pH 4,7	Citrat pH 5,9	Veronal pH 7,3	NH_3, NH_4Cl pH 8,5	Borat pH 8,6		Acetat pH 4,7	Citrat pH 5,9	Veronal pH 7,3	NH_3, NH_4Cl pH 8,5	Borat pH 8,6
1:1	1:1	1:1	1:1	1:1	Au	I	I	I	I	I
2:1	2:1	—	2:1	2:1	Ag	I	I	—	I	I
1:1	1:1	1:1	(1:1,5)	1:1	Hg	I	I	I	I	I
1:1	1:1	2:1	2:1	1:1	Phenyl-queck-silber	I	I	I	I	I
1:1	1:1	1:1	(1:1,5)	1:1	Cu	I	I	I	I	I
1:3	1:3	1:3	1:3	1:3	As	II	II	II	II	II
1:3	1:3	1:3	1:3	1:3	Sb	II	II	II	II	II
1:3	1:3	1:3	1:3	1:3	Bi	II	II	II	II	II
0	0	0	0	0	Tl	0	0	0	0	0
1:1	0	1:1	(1:1,5)	1:1	Ni	I	0	—	I	II
0	0	1:2	1:1,5	1:1	Co	0	0	I	I	I
0	0	1:2	1:2	1:2	Zn	0	0	II§	II	II
1:1	1:1	1:1,5	1:1,5	1:1,5	Cd	I	I	I	I	I
1:2	1:1,5	1:2	1:1,5	1:1,5	Pb	II	II	I	I	I

° Keine Komplexbildung.
† Aus polarometrischen Titrationen.
‡ Aus polarographischen Kurven.
§ pH 9.

Dimercaptopropanols und es bildet sich eine neue anodische Stufe bei positiveren Potentialen. Diese Stufe entspricht der freien SH-Gruppe der Verbindung (II). und ist durch Quecksilbersalzbildung an der Elektrodenoberfläche begrenzt (Abb. 6, 7, 8).

In der entstandenen Verbindung unterliegt das Zentralatom einer Reduktion, welche sich durch eine Stufe äussert, die bei negativeren Potentialen liegt als die Reduktionsstufe des freien Metalls (Tabelle 2).*

Ni^{II}, Co^{II}, Zn^{II} bilden bei niedrigeren pH-Werten keine Verbindungen mit Dimercaptopropanol (ähnlich wie Sulfide). Bei höheren pH-Werten bildet Zink

* Beim Arsen wird die Verbindung des Typus II in zwei Stufen reduziert. Das freie Arsen unterliegt unter den angewandten Bedingungen nicht der Reduktion.

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TABELLE 2. HALBSTUFENPOTENTIALE DER METALLE UND KOMPLEXE IN GEGENWART VON 2:3-DIMERCAPTOPROPANOL

Puffer	Acetat pH 4,7			Citrat pH 5,9			Veronal pH 7,3			NH_3, NH_4Cl pH 8,5			Borat pH 8,6		
Stufe / Metall	*Me*	K_a	K_r	*Me*	K_a	K_r	*Me*	K_a	K_r	*Me*	K_a	K_r	*Me*	K_a	K_r
As	→	−0,30	−0,55* −1,0	→	−0,25	−0,53 −1,0	→	−0,36	−0,63 −1,08	→	−0,5	−0,76 −1,20	→	−0,5	−0,75 −1,20
Sb	−0,35	−0,26	−0,57	−0,35	−0,24	−0,40	−0,42	−0,31	−0,63	−0,59	−0,49	−0,85	−0,85	−0,48	−0,81
Bi	−0,20	−0,17	−0,49	↓0,03	−0,05	−0,43 −1,30	−0,1§	−0,07	−0,50 −1,30	−0,31	−0,28‡	−0,65	−0,23§	−0,19	−0,68
Tl	−0,50	0	0	−0,50	0	0	−0,50	0*p*	0	−0,50	0*p*	0	−0,50	0*p*	0
Ni	−1,13	0	−0,80*t*	(−0,86)	0	0	—	—	—	−0,92	0	(−1,0)*t*	−1,10	0	(−1,0)*t*
Co	−1,38	0	−0,65	(−1,7)	0	0	−1,25	0	(−1,1)	−0,99 −1,14	0	(−1,1)	−0,90	0	(−1,1)
Zn	−1,10	0	0	−1,23	0	0	−1,15	−0,36	—	−1,09	−0,51	−1,16	−1,09	−0,45	—
Cd	−0,66	0	−1,06†	−0,61	0	Ndschl.	−0,60	0	(−0,83)*m*	−0,65	0	(−0,93)*m* Nsdchl.	−0,63	0	Ndschl.*m*
Pb	−0,51	−0,43	−0,61	−0,48	−0,35	−0,60	→	0	(−0,66)*m*	Ndschl.	0	(−0,7)*m* Ndschl.	Ndschl.	(−0,33)	−0,83*m*
$E_{\frac{1}{2}}$ (BAL)	−0,52			−0,50			−0,61			−0,79			−0,72		

* Verhältnis der Stufen verändert sich mit der Konzentration;
† bei höherer Konzentration gelangt es zur Bildung kolloidaler Lösungen;
‡ konzentrationsabhängig;
§ im Puffer allein eine zweite negativere Stufe des Wismuts sichtbar;
( ) schlecht ausgebildete Stufen, verändern sich mit der Zeit;
→ das Metall scheidet sich bis zuden Reduktionspotentialen der Teilchen des Grundelektrolyten nicht ab;
t gedehnte Stufe;
m kleine Stufe;
Me Stufe des Metalls;
K_a anodische Stufe des Komplexes;
K_r kathodische Stufe des Komplexes;
Ndschl. Niederschlag;
p teilweiser Abfall.

lösliche Verbindungen vom Typus (II), Nickel und Kobalt Chelatverbindungen vom Typus (I).

Tl^{I} reagiert im gesamten studierten pH-Bereich mit dem Dimercaptopropanol nicht. Seine Stufen addieren sich mit den Stufen des Dimercaptopropanols (Abb. 9).

Pb^{II}, Cd^{II} verhalten sich je nach den angewandten Bedingungen verschieden. Lösliche Verbindungen des Bleis mit freien SH-Gruppen entstehen bei pH < 6, bei Kadmium herrscht die Bildung wenig löslicher Komplexe vor.

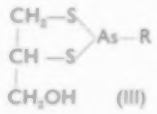
Fe^{III}, Sn^{II}. Die in Lösungen von Dimercaptopropanol nach Zugabe von zweiwertigem Zinn und dreiwertigem Eisen erhaltenen Kurven werden durch Oxydations Reduktionswirkungen dieser Metalle kompliziert. Das Verhalten von Sn^{II} nähert sich demjenigen des As^{III}, Sb^{III} und Bi^{III}.

As^{V}, Sb^{V} reagieren mit Dimercaptopropanol weder in anorganischen noch in organischen Verbindungen (wie in Phenylarson oder Kakodylsäure). Das Verhalten von "Neosalvarsan" und "Spironovan" ist durch die polarographische Aktivität der anwesenden Sulfoxylatgruppen kompliziert, man kann jedoch eine Reaktion dieser Verbindungen mit Dimercaptopropanol beobachten.

In Lösungen von Kobalt, Nickel, Eisen, Wismut und Arsen wurden Maxima bei −1,4 bis 1,6 V beobachtet, welche der katalytischen Wasserstoffabscheidung angehören.

Es handelt sich durchwegs um sehr feste Verbindungen, die manchmal fester als die entsprechenden Sulfide sind. Polarographisch können in solchen Fällen direkt nur die Zusammensetzung der Verbindung, jedoch nicht die Gleichgewichtskonstanten bestimmt werden.

Die wichtigste Folgerung dieser Arbeit ist die Aufklärung der Struktur der Verbindungen der Arsengruppe, die der Zusammensetzung der Merkaptide des Glutathions entspricht. Beim Lewisit und anderen Organoarsenverbindungen wurden nämlich cyklische Verbindungen (III) beschrieben[1,2,7,8,12] und eine ähnlich Konstitution wurde auch bei den anorganischen Verbindungen angenommen. Bei den Quecksilberverbindungen wurde im Einklang mit anderen Autoren[5,17,18] gefunden, dass je nach den Bedingungen verschiedene Verbindungen entstehen können. Zeitliche Veränderungen der Komplexe[18] konnten unter den gegebenen Bedingungen innerhalb einer Stunde weder bei den Quecksilberionen noch beim Phenylquecksilber nachgewiesen werden.



(III)

Es handelt sich in diesem Fall um das erste Beispiel, bei dem aus der anodischen Stufe der im Komplex gebundenen Liganden auf die Zusammensetzung des Komplexes geschlossen wurde.

Der Einfluss der Eiweissstoffe auf die Reaktion zwischen Dimercaptopropanol und Metallen

Weiter wurde untersucht. ob eine Zugabe von Dimercaptopropanol die Metalle aus ihrer Bindung an Proteine freimachen kann. Zu diesem Zwecke wurde Albumin

aus Pferdeserum gewählt, denn bei diesem Protein wurde eine ziemlich feste Bindung der Metalle an Thiol- und andere funktionelle Gruppen festgestellt.[26]

Zu einer gepufferten Metallösung wurde das Albumin in einer so grossen Konzentration zugegeben, dass die Metallstufe völlig unterdrückt wurde. Nach Zugabe von Dimercaptopropanol wuchsen auf den polarographischen Kurven die Reduktionsstufen (und in manchen Fällen auch die anodischen Stufen), welche den löslichen Verbindungen des Metalls mit dem Dimercaptopropanol entsprechen (Abb. 10). Quantitative Messungen in diesen Reaktionsgemischen wurden dadurch erschwert, dass das Eiweiss die Metallstufen nicht nur durch Bindung, sondern auch durch seine Oberflächenaktivität unterdrückt. Auch die Stufen der Metall-Dimercaptopropanol Verbindungen wurden durch die Oberflächenaktivität unterdrückt (Abb. 11). Trotzdem konnte ermittelt werden, dass zur Lockerung der Metalle aus ihrer Bindung an Proteine praktisch eine äquimolare Menge des Dimercaptopropanols genügt (d.h. z.B. beim Arsen ein Dreifaches der Metallkonzentration). Der Typus der Verbindungen zwischen Dimercaptopropanol and den Metallen war durch die Anwesenheit der Proteine nicht beeinflusst. Nur die Löslichkeit der kolloidalen Substanzen vom Typus I wurde erhöht.

Einfluss der Oxydationsmittel

Nach den oben erwähnten Ergebnissen sollte bei Intoxikationen eine sehr kleine Tagesdosis des Dimercaptopropanols genügen, die Spuren der Schwermetalle aus dem Organismus abzuscheiden. Nach den klinischen Erfahrungen ist jedoch, wie bereits oben erwähnt wurde (S), das Gegenteil der Fall, und es müssen sehr grosse Tagesdosen gegeben werden. Der Grund hierfür wurde darin gesucht, dass nur ein sehr kleiner Teil des Dimercaptopropanols in wirksamer Form ausgenützt wird. Der Rest unterliegt im Organismus Veränderungen hauptsächlich durch Oxydation, durch welche das Dimercaptopropanol inaktiviert wird.

Deshalb wurden einige Modellreaktionen studiert, und zwar die Oxydation durch Sauerstoff, Wasserstoffperoxyd und Cystin und die Reaktion mit Chinon.

Oxydation durch Sauerstoff und Wasserstoffperoxyd. Bei der Oxydation wässriger Lösungen von Dimercaptopropanol durch Sauerstoff bei grösseren pH-Werten als etwa 6 wurde gefunden, dass bei der Reaktion Wasserstoffperoxyd entsteht, welches weiter mit dem Dimercaptopropanol reagiert (S). Bei der Oxydation durch Sauerstoff entsteht ein Disulfid, das weiter zu einer wasserunlöslichen Verbindung oxydiert wird. Diese komplizierte Folge von Reaktionen, teilweise wahrscheinlich mit Radikalmechanismus,[27] wurde z.Z. nicht eingehender studiert und es wurde nur konstatiert, dass die Oxydationsgeschwindigkeit mit steigendem pH-Wert (d.h. mit steigender Dissoziation des Dimercaptopropanols) steigt.

Flüssiges Dimercaptopropanol (Substanz) unterliegt dagegen bei Aufbewahrung an der Luft auch bei erhöhter Temperatur innerhalb von 20 Tagen nicht der Oxydation.

Nach der Zugabe von Wasserstoffperoxyd nimmt die anodische Stufe des Dimercaptopropanols ab. Auf Kosten der Wasserstoffperoxydstufe wächst eine Reduktionsstufe des Disulfids des Dimercaptopropanols. Diese Stufe hat praktisch dasselbe Halbstufenpotential wie die anodische Stufe der Thiolform. Aus der zeitbedingten Abnahme der anodischen Stufe des Dimercaptopropanols (Abb. 12) wurde für die

[26] z. B. I. M. Klotz, J. M. Urquart und H. A. Fiess *J. Amer. Chem. Soc.* **74,** 5537 (1952).
[27] G. Barron und U. Flood *J. Gen. Physiol.* **33,** 229 (1950).

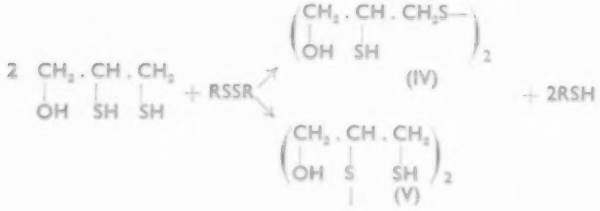
Reaktion zweiter Ordnung zwischen Wasserstoffperoxyd und Dimercaptopropanol in Boratpufferlösung vom pH 9,3 bei 20°C die Reaktionsgeschwindigkeitskonstante $k = 4$ l/mol s gefunden. Folgereaktionen[28] machen sich nur bei Wasserstoffperoxydüberschuss geltend.

Reaktionen des Dimercaptopropanols mit Cystin. Nach den Angaben der Literatur reduziert 2:3-Dimercaptopropanol die disulfidischen Gruppen des Insulins[29] und unterliegt so einer der häufigsten Reaktionen zwischen Thiol und Disulfid, die sich in Organismen abspielen.[28,30–34] Empirisch wurde gefunden,[35] dass die Verabreichung des 2:3-Dimercaptopropanols auch bei gewissen Nervenerkrankungen, bei welchen ein erhöhter Cystinspiegel vorliegt, zweckmässig ist.

Nach Zugabe des Cystins zu einer gepufferten Dimercaptopropanollösung entsteht auf Kosten der Stufe des Dimercaptopropanols eine neue anodische Stufe, bei einem um 300 mV positiveren Halbstufenpotential (Abb. 13). Diese Stufe entspricht der Summe der anwesenden Monothiolverbindungen (d.h. des Cysteins aus Cystin und der Thiolverbindung (IV) oder (V), welche durch teilweise Oxydation des Dimercaptopropanols entsteht).

Die Stufe der Monothiolverbindung wächst mit der Zeit an (Abb. 13). Dabei steigt die Dimercaptopropanolstufe über die Galvanometernullinie hinaus. Dass die Monothiolstufen mit der Konzentration des zugefügten Cystins steigen, ist aus Abb. 14 ersichtlich (die nach dem Reaktionsablauf registriert wurde).

Die Reaktion lässt sich am besten in einem Boratpuffer vom pH-Wert 9,3 studieren. Die anodische Stufe ist am höchsten, wenn die Konzentration des Cystins die Hälfte der Dimercaptopropanolkonzentration beträgt. Es muss also ein Mol Cystin (RSSR) mit zwei Molen 2:3-Dimercaptopropanol reagieren. Für das Schema der Bruttoreaktion bleibt also die einzige Möglichkeit

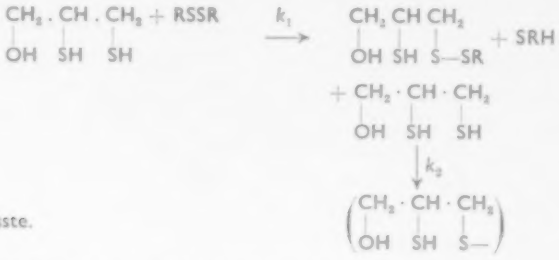


Die Entstehung eines inneren Disulfids oder von Mischdisulfiden, bei welchen ein Mol Dimercaptopropanol mit einem oder sogar mit zwei Molen des Cystins reagieren muss, kann abgelehnt werden.

Bei der Untersuchung der Kinetik dieser Reaktion wurde jedoch gefunden, dass der geschwindigkeitsbestimmende Schritt eine Reaktion zweiter Ordung mit der Reaktionsgeschwindigkeitskonstante $k_1 \approx 7$ l/mol s (bei pH 9,3 und 20°C) ist.

[28] M. Calvin *Glutathione* S. 3 Academic Press, New York (1954).
[29] G. Barron, Z. B. Miller und J. Meyer *Biochem. J.* **41**, 78 (1947).
[30] J. M. Kolthoff, W. Stricks und R. C. Kapoor *J. Amer. Chem. Soc.* **77**, 4733 (1955).
[31] T. Wieland *Glutathione* S. 45. Academic Press, New York (1954).
[32] B. Vennesland und E. E. Conn *Glutathione* S. 105 Academic Press, New York (1954).
[33] E. Racker *Glutathione* S. 165 Academic Press, New York (1954). (Diskussionsbeitrag von E. S. G. Barron.)
[34] H. Neurath und K. Bailey *The Proteins* Band I. S. 913. Academic Press, New York (1953).
[35] J. Teisinger Privatmitteilung.

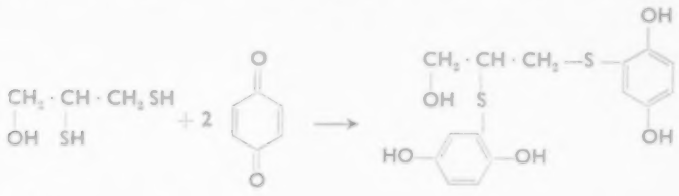
Der Reaktionsmechanismus könnte z.B. der folgende sein:



wo $k_2 \gg k_1$ sein müsste.

Die Kinetik dieser Reaktion wird weiter studiert. Bei Cystinüberschuss (Abb. 14, Kurve 5) nimmt die Höhe der Monothiolstufe ab. Monothiolverbindungen unterliegen einer weiteren Reaktion mit Cystin.

Reaktion des Dimercaptopropanols mit Chinon. Ähnlich wie bei anderen Thiolverbindungen[36] verläuft auch bei Dimercaptopropanol in Gegenwart von Chinon eine schnelle 1:4-Addition. Die anodische Stufe des 2:3-Dimercaptopropanols verschwindet beim Verhältnis 1 Mol Dimercaptopropanol: 2 Molen Chinon (Abb. 15). Auf der Kurve entsteht keine Stufe des Disulfids. Weil endlich keine neue anodische Stufe einer Monothiolverbindung (S), sondern lediglich die Stufe des Hydrochinons entsteht, kann der Reaktion nur folgendes Schema beigeordnet werden:



Schlussfolgerung

Es war möglich, die Bildung, die Bedingungen der Entstehung und die Zusammensetzung der Verbindungen von Dimercaptopropanol mit Schwermetallen polarographisch zu beweisen. Die gebildeten Verbindungen sind viel fester als die Bindung der Metalle an Proteine. Bereits eine äquivalente Menge des Dimercaptopropanols genügt zur Lockerung praktisch des gesamten Metalls. Der notwendige grosse Dimercaptopropanolüberschuss, welcher bei Intoxikationen durch Schwermetalle injiziert werden muss, ist dadurch begründet, dass das Dimercaptopropanol im Organismus der Reaktion mit verschiedenen Oxydationsmitteln unterliegt. Von den Reaktionen, die zur Inaktivierung des Dimercaptopropanols führen könnten, wurde der Verlauf der Oxydation durch Wasserstoffperoxyd und Cystin sowie die Reaktion mit Chinon, wo sich eine 1:4-Addition abspielt, bestimmt.

ZUSAMMENFASSUNG

(1) 2:3-Dimercaptopropanol (BAL) äussert sich auf den polarographischen Kurven durch eine anodische Stufe, welche einer Quecksilbersalzbildung entspricht. Bei höheren Konzentrationen als etwa 2×10^{-4}M machen sich Adsorptionserscheinungen geltend.

[36] G. H. Meguerrian *J. Amer. Chem Soc.* 77, 5019 (1955).

(2) Mit Hilfe dieser Stufe und weiter der Reduktions- bzw. anodischen Stufe der Komplexverbindung wurde die Zusammensetzung der Verbindungen zwischen Dimercaptopropanol und Schwermetallen studiert. Die Metalle der ersten analytischen Gruppe bilden unlösliche Chelatverbindungen, die der Arsengruppe lösliche. Das Verhalten anderer Metalle hängt von den Bedingungen ab.

(3) Es wurde bestätigt, dass die Zugabe von Dimercaptopropanol die Metalle aus ihrer Bindung an Eiweissstoffe freimachen kann. Zur Lockerung der Metalle genügt praktisch eine äquimolare Menge des Dimercaptopropanols.

(4) Die grossen Tagesdosen des Dimercaptopropanols bei der klinischen Behandlung der Intoxikationen durch Schwermetalle wurden durch Inaktivierung des grössten Teiles des Dimercaptopropanols im Organismus erklärt. Es wurden einige Modellreaktionen für diese Inaktivierung studiert.

(5) Bei der Oxydation durch Sauerstoff entsteht bei pH > 6 Wasserstoffperoxyd, das weiter mit Dimercaptopropanol in einer Reaktion zweiter Ordnung unter Entstehung des Disulfids reagiert.

(6) Durch Reaktion des Dimercaptopropanols mit Cystin entstehen neben Disulfiden auch Monothiolverbindungen. Der geschwindigkeitsbestimmende Schritt ist eine Reaktion zweiter Ordnung.

(7) Durch Reaktion des Benzochinons mit Dimercaptopropanol verschwindet die anodische Stufe des Dimercaptopropanols. Es entsteht kein Disulfid, sondern es findet eine 1:4-Addition statt. Ein Mol Dimercaptopropanol reagiert mit 2 Molen Chinon. An der Reaktion, die bei pH 4 bis 7 schnell verläuft, nehmen beide SH-Gruppen des Dimercaptopropanols teil.

Tetrahedron, 1957, Vol. 1, pp. 301–309. Pergamon Press Ltd., London

VOL.
1
1957

AN ALKALOID OF *DIOSCOREA HISPIDA*, DENNSTEDT—IV*

FURTHER INVESTIGATIONS ON THE LACTONE RING

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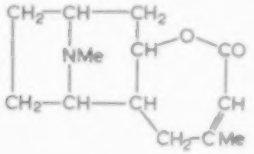
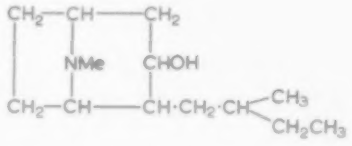
(*Received* 6 *August* 1957)

Abstract—Reductive degradation of the lactone ring of dioscorine has yielded a saturated tertiary alcohol, the formation of which means that the previously proposed formula (I) for the alkaloid is incorrect. The lactone and tropane systems are linked in a *spiro* manner, as in (VI) or (VII), of which the former is preferred for dioscorine. The behaviour of the alkaloid on Hofmann degradation can be explained on the basis of structure (VI). From infra-red studies on the above tertiary alcohol dioscorine is derived from 7α-hydroxytropane, and the (–)-base is therefore (XX) or its optical enantiomorph.

THE presence in dioscorine, an alkaloid of *Dioscorea hispida*, Dennstedt, of a tropane system linked with an αβ-unsaturated lactone ring has been established in previous parts of this series.[1,2] Infra-red absorption studies on the alkaloid and its dihydro-derivative[1] showed that the lactone ring was 6- or higher-membered, and not 5-membered, as originally proposed by Gorter.[3] On the basis of Hofmann and other degradations structure (I) has recently been proposed for dioscorine.[4] The investigations described below, which are concerned with the reductive degradation of the lactone ring, show that this formula must be modified.[5]



(I)



(II)

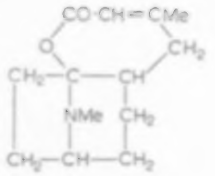
Reduction of dioscorine with lithium aluminium hydride affords *dioscorinol*, $C_{13}H_{23}O_2N$, an unsaturated glycol resulting from the reductive cleavage of the lactone ring without attack of the ethylenic bond. The presence of an ethylenic bond was confirmed by the infra-red absorption of the diol, and by ozonolysis, which gave glycollic aldehyde, identified as the *p*-nitrophenylosazone. This establishes the presence of the grouping $>C{=}CH{\cdot}CH_2OH$ in dioscorinol, and is consistent with the results of oxidative degradation of the alkaloid described earlier.[4] Accompanying

* Part III, *J. Chem. Soc.* 1577 (1956).
[1] A. R. Pinder *Nature, Lond.* **168**, 1090 (1951); *J. Chem. Soc.* 2236 (1952).
[2] A. R. Pinder *J. Chem. Soc.* 1825 (1953).
[3] M. K. Gorter *Rec. Trav. Chim. Pays-Bas* **30**, 161 (1911).
[4] A. R. Pinder *J. Chem. Soc.* 1577 (1956).
[5] For a preliminary communication, see A. R. Pinder *Chem. and Ind.* 1240 1957.

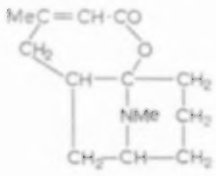
glycollic aldehyde was a basic keto-alcohol, the examination of which will be described in a future communication. This compound gives a positive iodoform reaction, and therefore contains a CH_3CO— group, which confirms the presence of a methyl group in the β-position of the lactone ring in dioscorine. On catalytic hydrogenation under mild conditions dioscorinol affords dihydrodioscorinol, identical with the product obtained by the reduction of dihydrodioscorine with lithium aluminium hydride.[5]

That dioscorinol is an allylic alcohol containing an α-hydrogen atom was confirmed by hydrogenolysis of the base. This was accomplished either by reduction with sodium and ethanol in liquid ammonia[6] or with a platinum catalyst.[7] In the former case the main product was *deoxydioscorinol*, $C_{15}H_{23}ON$, with some dihydrodioscorinol. Deoxydioscorinol on permanganate oxidation or ozonolysis afforded acetaldehyde, indicating the presence of the grouping $>C{=}CH{\cdot}CH_3$, derived by hydrogenolysis of the allylic hydroxyl group in dioscorinol. Hydrogenolysis with a platinum catalyst occurred more slowly, but the final product was the saturated base *dihydrodeoxydioscorinol*, $C_{15}H_{25}ON$, which was also readily obtained by the catalytic hydrogenation of deoxydioscorinol.

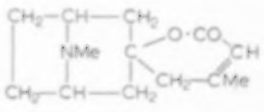
Dihydrodeoxydioscorinol was recovered unchanged when the base was heated at 65–70° for several hours with chromic acid in acetic acid solution, and it was not converted into an *O*-acetate on treatment with acetic anhydride and pyridine. Further, the base was readily dehydrated under mild conditions to *anhydrodihydrodeoxydioscorinol*, $C_{15}H_{23}N$. It is evident, therefore, that dihydrodeoxydioscorinol is a tertiary alcohol, so that dioscorine cannot be represented by (I), which would yield the secondary alcoholic dihydrodeoxy-base (II). Structures such as (III) and (IV) for the alkaloid would give tertiary alcoholic dihydrodeoxy-bases, but these formulae may be ruled out because dioscorinol, deoxydioscorinol and dihydrodeoxydioscorinol do not have the properties of an α-carbinolamine.



(III)



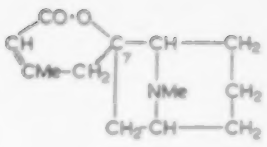
(IV)



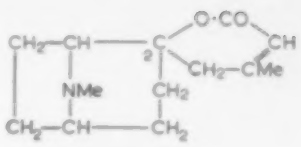
(V)

It is apparent, therefore, that in dioscorine the tropane system and lactone ring must be linked in a *spiro* manner, as in structures (V), (VI) and (VII). Of these, (V) would seem to be the most acceptable in that it is derived from tropine, the parent hydroxy-base of many well-known alkaloids.[8] This structure must, however, be rejected on the grounds that dioscorine and the transformation products described are all optically active, whereas (V) and the structures derived from it by the reactions outlined each have a plane of symmetry.

[6] A. J. Birch *J. Chem. Soc.* 809 (1945); *Quart. Rev. Chem. Soc.* **4**, 69 (1950); A. J. Birch and A. R. Murray *J. Chem. Soc.* 1888 (1951).
[7] J. Weinstock and V. Boekelheide *J. Amer. Chem. Soc.* **75**, 2546 (1953).
[8] T. A. Henry *The Plant Alkaloids* (4th Ed.) pp. 64–115. Churchill, London (1949).



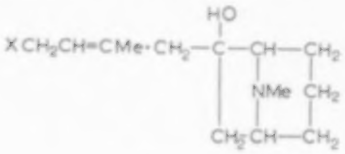
(VI)



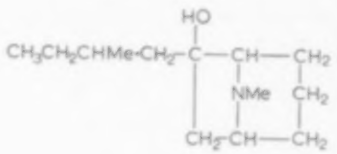
(VII)

Of the two structures (VI) and (VII), the former is more likely to represent dioscorine, on the grounds that it is derived from 7-hydroxytropane, and several familiar alkaloids are known to have structures derived from this base (*e.g.* scopolamine,[9] meteloidine[10]). On the other hand, as yet no alkaloid is known having a structure derived from 2-hydroxytropane, to which base structure (VII) is related. Formula (VI) is therefore advanced for dioscorine, and efforts are now being made to substantiate this view by synthesis.

On the basis of formula (VI) for dioscorine, dioscorinol is (VIII, X = OH), deoxydioscorinol (VIII, X = H), and dihydrodeoxydioscorinol (IX).* Anhydrodihydrodeoxydioscorinol is probably a mixture of the double-bond isomerides (X) and (XI), the third possible mode of dehydration of (IX) being ruled out by the fact

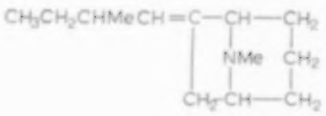


(VIII)

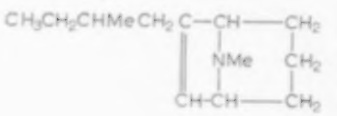


(IX)

that the anhydro-base has not the properties of a vinylamine. *Anhydrotetrahydrodeoxydioscorinol*, obtained by catalytic hydrogenation of the anhydro-base, is then

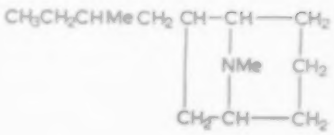


(X)



(XI)

7-(2′-methyl-*n*-butyl) tropane (XII).



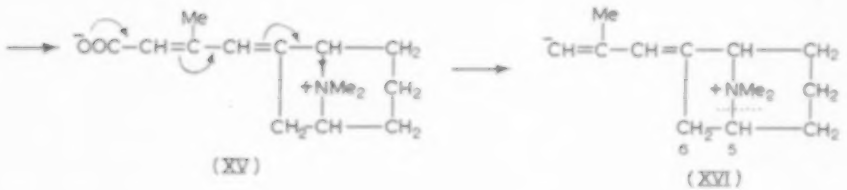
(XII)

In an earlier communication[2,3] the behaviour of dioscorine on Hofmann degradation has been described. A deep-seated decomposition occurs, with the elimination of carbon dioxide and the formation of an oxygen-free base $C_{13}H_{21}N$. This

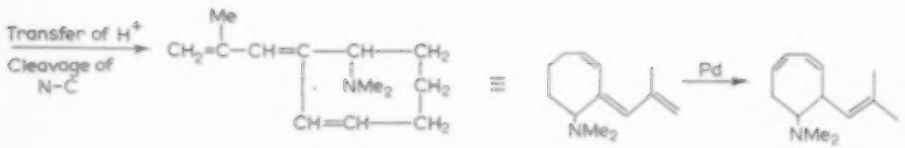
[9] T. A. Henry *The Plant Alkaloids* (4th Ed.) p. 84. Churchill, London (1949).
[10] A. Heusner *Chem. Ber.* **87**, 1032 (1954).

unusual mode of decomposition, which is reminiscent of the behaviour of dihydro-β-erythroidine on Hofmann degradation,[11] may possibly be explained on the basis of formula (VI) for dioscorine as follows. Dioscorine methohydroxide is probably an equilibrium mixture of the quaternary hydroxide (XIII) and the betaine (XIV); it cannot be entirely the betaine form because the compound in aqueous solution is strongly basic. The first stage in the decomposition is probably the elimination of water from the tertiary alcoholic betaine (XIV), via the side-chain methylene group,

(XIII) (XIV)



(XV) (XVI)



(XVII) (XVIII)

the hydrogen atoms of which are activated by conjugation with the carboxyl group, giving (XV). In this structure the strongly electron-attracting quaternary ammonium cation is now able, by the mechanism shown along the conjugated system, to facilitate the decarboxylation of the acid to the intermediate structure (XVI),[12] which is stabilised by transfer of a proton from $C_{(6)}$ to the terminal carbon atom of the side-chain, and cleavage of the N—$C_{(5)}$ bond. These stages are facilitated by the tendency to form the extended conjugated system in XVII), which therefore represents the constitution of the $C_{13}H_{21}N$ base. The chemical properties of the base, however, showed it to be a mixture,[2] and (XVII) is therefore in all probability the main constituent. It is conceivable, especially in the presence of an active catalyst at a high temperature, that double bond isomers such as (XVIII) will also be present in the base, and this

* A good *C*-methyl analysis for this compound could not be obtained [compare E. J. Eisenbraun, S. M. McElvain and B. F. Aycock *J. Amer. Chem. Soc.* **76**, 607 (1954)].

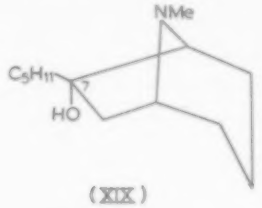
[11] V. Boekelheide, J. Weinstock, M. F. Grundon, G. L. Sauvage and E. J. Agnello *J. Amer. Chem. Soc.* **75**, 2550 (1953).

[12] B. R. Brown *Quart. Rev. Chem. Soc.* **5**, 131 (1951).

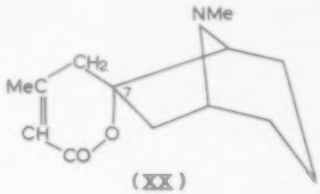
accounts for the ready formation of $\beta\beta$-dimethylstyrene and *iso*butylbenzene when the base $C_{13}H_{21}N$ is heated with palladised charcoal, as explained earlier.[4]

It is interesting to note that dihydrodioscorine, when subjected to Hofmann degradation, yields a normal *des*-base; this would be expected because the γ-methylene group is not activated by conjugation with the carbonyl group as in dioscorine, and the mechanism described above cannot operate.

A careful study, under high resolution conditions, of the infra-red absorption spectrum of dihydrodeoxydioscorinol (IX) in carbon tetrachloride solution showed a single band at 3651 cm^{-1}, with no internal hydrogen bonding; under the same conditions tropine showed a similar band at 3653 cm^{-1}, again with no intramolecular hydrogen bonding.[13] It is concluded that dihydrodeoxydioscorinol has an α-oriented hydroxyl group, and is therefore more accurately represented by (XIX). It is to be expected that the lithium aluminium hydride reduction of dioscorine, which involves



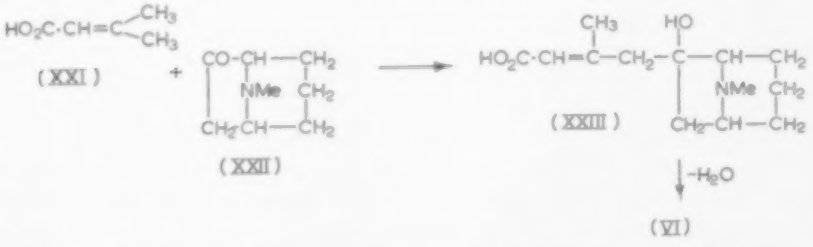
(XIX)



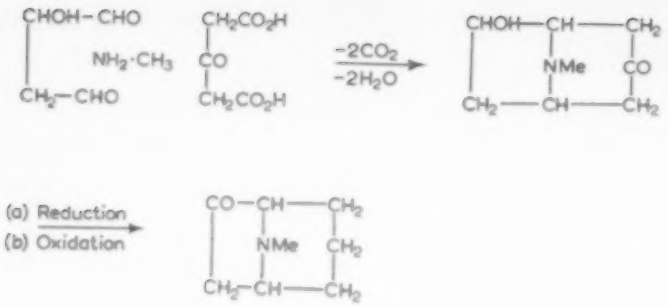
(XX)

the cleavage of the carbonyl-oxygen bond, will not disturb the stereochemistry at $C_{(7)}$, so that dioscorine is represented by (XX).

From the biogenetic point of view it would seem reasonable that dioscorine is formed by an aldol-type condensation between 7-ketotropane (XXII) and senecioic acid (XXI), which occurs in nature,[14] to give the hydroxy-acid (XXIII), the methyl groups of senecioic acid being activated by conjugation with the carbonxyl group. Lactonisation of the hydroxy-acid affords dioscorine (VI). The view that senecioic acid is involved in the biosynthesis of dioscorine is strengthened by the fact that tropine senecioate has recently been found to occur to a small extent in the tubers of *D. hispida*. The biosynthesis of (XXII) presents a problem, there being as yet no knowledge of the way in which hydroxytropanes, other than tropine, are formed in the plant.[15] The ketone may arise from malic dialdehyde via a Robinson tropinone synthesis, [16] with subsequent reduction and oxidation:—



[13] B. L. Zenitz, C. M. Martini, M. Priznar and F. C. Nachod *J. Amer. Chem. Soc.* **74,** 5564 (1952).
[14] Y. Asahina *Arch. Pharm.* **251,** 355 (1913).
[15] Sir R. Robinson *The Structural Relations of Natural Products* p. 63. Oxford University Press (1955).
[16] Sir R. Robinson *J. Chem. Soc.* **111,** 762 (1917); J. C. Sheehan, and B. M. Bloom *J. Amer. Chem. Soc.* **74,** 3825 (1952); A. Stoll, B. Becker and E. Jucker *Helv. Chim. Acta* **35,** 1263 (1952).



(XXII)

EXPERIMENTAL

Lithium aluminium hydride reduction of dioscorine. A suspension of powdered lithium aluminium hydride (0·6 g) in dry ether (150 cm³) was added during 30 min at room temperature with shaking to dioscorine (2·0 g) in dry ether (50 cm³). After keeping for 18 hr the reaction mixture was decomposed by the careful addition of water, in the presence of "Celite". The ethereal solution was decanted, dried (potassium carbonate) and evaporated. The residual thick syrup was distilled in a bulb-tube, giving *dioscorinol* (VIII, X = OH) (1·7 g), b.p. 175° (bath)/1 mm, 155–160° (bath)/0·2 mm, 150° (bath)/0·05 mm, $[\alpha]_D^{20}$ + 1·9° (c 6·2 in chloroform) (Found: C, 69·6, 69·5; H, 10·4, 10·2. $C_{13}H_{23}O_2N$ requires C, 69·3; H, 10·2 per cent) as a glassy solid. Infra-red absorption (in carbon tetrachloride): broad band at 3360 (associated OH), band at 1653 (C=C), and at 805 cm^{-1} (R_1R_2C=CHR_3). Dioscorinol is readily soluble in water, giving a strongly alkaline solution; it is sparingly soluble in ether and moderately so in chloroform. The *picrate* separated from methanol in yellow nodules, m.p. 159-160° (decomp.) (Found: C, 50·2; H, 5·8. $C_{19}H_{26}O_9N_4$ requires C, 50·2; H, 5·8 per cent). The *picrolonate* crystallised from ethanol in clusters of pale yellow prisms, m.p. 212° (decomp.) (Found, on material dried at 100° *in vacuo*, C, 56·4; H, 6·3. $C_{23}H_{31}O_7N_5$ requires C, 56·4; H, 6·3 per cent). Attempts to make the hydrochloride, hydrobromide, and methiodide gave oily products.

Ozonolysis of dioscorinol. A solution of dioscorinol (4·0 g) in glacial acetic acid (15 cm³) was cooled to 10° and ozonised at this temperature for 4 hr. The solution was diluted with ether (100 cm³) and shaken with zinc dust (6·0 g) for 3 hr, after which time the starch-iodide test was negative. The ether was removed under reduced pressure at 15–20°, and the residue treated with water (30 cm³), filtered, and mixed with a concentrated ethanolic solution of *p*-nitrophenylhydrazine (4·0 g). After warming the solution on the water-bath for 30 min the precipitate was collected, washed with water and dried. Crystallisation from nitrobenzene gave wine-red needles (0·65 g), m.p. 310–311° (decomp.) alone or mixed with an authentic specimen of glyoxal bis-*p*-nitrophenylhydrazone (m.p. 311°),[17] obtained from glycollic aldehyde prepared by the ozonolysis of allyl alcohol.[18]

Reduction of dioscorinol. (a) Dioscorinol (0·5 g) in ethanol (10 cm³) was shaken in hydrogen at room temperature and pressure with 5 per cent palladised charcoal

[17] A. Wohl and C. Neuberg *Ber. Dtsch. Chem. Ges.* **33**, 3107 (1900).
[18] H. O. L. Fischer and L. Feldman *Ber. Dtsch. Chem. Ges.* **62**, 854 (1929).

(0·5 g; Baker Platinum Co.). After 2 hr absorption had ceased (1 mol absorbed), and the solution was filtered and evaporated. The residue distilled at 160–165° (bath)/0·05 mm (0·5 g). The picrate had m.p. 144°, with previous softening at 138°, alone or mixed with the picrate of dihydrodioscorinol, obtained by the lithium aluminium hydride reduction of dihydrodioscorine.[2]

(b) Dioscorinol (2·6 g) in ethanol (15 cm^3) was added to liquid ammonia (300 cm^3), and the solution stirred vigorously during the gradual addition of sodium (3·0 g) in small pieces over 30 min. After stirring for a further 30 min, 75 cm^3 of water was added cautiously, dropwise, and the ammonia allowed to evaporate overnight. A few pellets of potassium hydroxide were added, the solution extracted thoroughly with ether, and the extract dried with potassium carbonate. Evaporation of the solvent gave a syrup, which was separated by distillation into two fractions. The main fraction, distilling at 123–125° (bath)/0·3 mm, 97–98° (bath)/0·1 mm, 87–88° (bath)/0·04 mm (1·6 g) $[\alpha]_D^{24} + 23{\cdot}0°$ (*c* 2·3 in chloroform) (Found: C, 74·3; H, 11·4; N, 6·9. $C_{13}H_{23}ON$ requires C, 74·6; H, 11·0; N, 6·7 per cent) was *deoxydioscorinol* (VIII, X = H). Infra-red absorption (in carbon disulphide): bands at 3598 (non-bonded hydroxyl), 2804 (*N*-methyl), 823, 806, and 754 cm^{-1} (trisubstituted ethylenic bond). Deoxydioscorinol is a strong base, slightly soluble in water. The *methiodide*, prepared by mixing the base with an excess of methyl iodide, was formed very readily and crystallised from a large volume of acetone in clusters of elongated prisms, m.p. 191·5–192° (Found: C, 48·2; H, 7·6. $C_{14}H_{26}ONI$ requires C, 47·9; H, 7·4). The *picrate* separated from methanol in glistening yellow elongated prisms, m.p. 112·5° (Found: C, 51·8; H, 6·0; N, 12·7. $C_{19}H_{26}O_8N_4$ requires C, 52·05; H, 5·9; N, 12·8 per cent).

A higher-boiling fraction distilled at 160–165° (bath)/0·05 mm (0·75 g). It was converted to its picrate, which crystallised from methanol in yellow prisms, m.p. 144°, with previous softening at 138°, alone or mixed with a specimen of dihydrodioscorinol picrate.[2]

Dihydrodeoxydioscorinol (*IX*). (a) Dioscorinol (2·55 g) dissolved in *N* hydrochloric acid (40 cm^3) was shaken in hydrogen at room temperature and pressure with pre-reduced platinic oxide catalyst (0·4 g) (Baker Platinum Co.) until absorption ceased (about 6 hr; 2 mols. absorbed). The solution was filtered, basified with potassium hydroxide and extracted with ether. Evaporation of the dried (potassium carbonate) extract gave *dihydrodeoxydioscorinol* (IX), which distilled at 104–105° (bath)/0·15 mm (2·45 g), $[\alpha]_D^{20} + 21{\cdot}3°$ (*c*, 2·35 in chloroform) (Found: C, 73·6; H, 11·7; N, 6·3, CMe, 5·1. $C_{13}H_{25}ON$ requires C, 73·9; H, 11·8; N, 6·6; 2CMe, 14·2 per cent). Infra-red absorption (in carbon tetrachloride): single hydroxyl band at 3651 cm^{-1}, with no internal hydrogen bonding. Dihydrodeoxydioscorinol is a strong base, slightly soluble in water. The *methiodide*, obtained by mixing the base with methyl iodide, separated from acetone-light petroleum (b.p. 80–100°) in clusters of prisms, m.p. 162° (Found, on material dried at 100° *in vacuo*: C, 47·4; H, 7·7; N, 3·9. $C_{14}H_{28}ONI$ requires C, 47·6; H, 7·9; N, 4·0 per cent). The *picrate*, prepared in methanol solution, crystallised from methanol in glistening yellow plates, m.p. 107·5–108° (Found, on material dried at 78° *in vacuo*: C, 51·8; H, 6·7; N, 12·9. $C_{19}H_{28}O_8N_4$ requires C, 51·8; H, 6·4; N, 12·7 per cent).

(b) Deoxydioscorinol (0·5 g) in *N* hydrochloric acid (15 cm^3) was shaken with pre-reduced platinic oxide catalyst (0·1 g) in hydrogen at room temperature and

pressure. After 2 hr absorption (1 mol) had ceased. The solution was filtered, basified, and extracted with ether. Evaporation of the dried extract gave dihydrodeoxydioscorinol, b.p. 100–101° (bath)/0·1 mm (0·5 g), picrate m.p. 107·5–108° and methiodide m.p. 162°, both alone or mixed with the respective derivatives obtained as in (a) above. Identity was confirmed by comparison of the infra-red curves of the two bases.

Dihydrodeoxydioscorinol was recovered unchanged when heated at 65–70° in glacial acetic acid solution for 2½ hr with chromic acid, and also when warmed with acetic anhydride in the presence of pyridine.

Oxidation of deoxydioscorinol (a) Deoxydioscorinol (0·1 g) in 5 per cent sulphuric acid (50 cm³) was heated to boiling and a 1·5 per cent aqueous solution of potassium permanganate (80 cm³) added dropwise during 5 min, the boiling being maintained whilst about 35 cm³ of distillate were collected in an ice-cooled receiver.[19] The distillate was mixed with an excess of a saturated solution of 2:4-dinitrophenylhydrazine in dilute sulphuric acid and kept for several hours. The yellow precipitate was collected, washed with water, dried, and crystallised from ethanol, from which it separated in orange-yellow needles m.p. 167–168°, alone or mixed with an authentic specimen of acetaldehyde 2:4-dinitrophenylhydrazone (m.p. 168°). Later fractions of the distillate gave formaldehyde 2:4-dinitrophenylhydrazone, identified as previously,[1] arising from oxidation of the *N*-methyl group.

(b) Deoxydioscorinol (2·0 g) in glacial acetic acid (15 cm³) was ozonised at 0–5° for 3 hr. Water (10 cm³) was added, followed by zinc dust (4·0 g), and the mixture shaken for 2–3 hr. The filtered solution was mixed with excess of a saturated solution of 2:4-dinitrophenylhydrazine in dilute sulphuric acid and kept for several hours. The precipitate was collected and identified as acetaldehyde 2:4-dinitrophenylhydrazone as in (a).

Anhydrodihydrodeoxydioscorinol (X) or (XI). A solution of dihydrodeoxydioscorinol (0·5 g) in dry ether (5 cm³) was added dropwise to thionyl chloride (1 g) in dry ether (5 cm³), the reaction being conducted at 0–10° during 10 min, with continuous shaking. Finally the mixture was heated under reflux in a bath at 45–50° for 30 min. The solvent was evaporated, the excess thionyl chloride removed *in vacuo*, and the syrupy residue taken up in water, a neutral turbidity being removed with ether. Evaporation of the dried extract gave the *anhydro-base*, b.p. 124°/18 mm, 128°/21 mm (0·35 g) (Found: C, 80·5; H, 11·5; N, 7·3. $C_{13}H_{23}N$ requires C, 80·8; H, 11·9; N, 7·25 per cent). Infra-red absorption (liquid film): probably at least two types of C=C bond present; bands at 1635 and 1665 cm^{-1} The *picrate* crystallised from 50 per cent ethanol in glistening, yellow needles, m.p. 118° (Found: C, 54·1; H, 6·1. $C_{19}H_{26}O_7N_4$ requires C, 54·0; H, 6·2 per cent).

Anhydrotetrahydrodeoxydioscorinol (XII). The foregoing anhydro-base (0·35 g) in glacial acetic acid (15 cm³) was shaken with pre-reduced platinic oxide catalyst (50 mg) in hydrogen at room temperature and pressure for 12 hr. The absorption (1 mol) had then ceased. The solution was filtered, basified, and extracted with ether. Evaporation of the dried extract gave *anhydrotetrahydrodeoxydioscorinol*, b.p. 135°/24–25 mm (0·35 g). (Found: C, 80·1; H, 7·7. $C_{13}H_{25}N$ requires C, 80·0; H, 7·8 per cent). The base was stable to cold, acid potassium permanganate. The *picrate* separated from 50 per cent methanol in glistening yellow needles, m.p. 116° (Found: C, 53·5; H, 6·7; N, 13·0. $C_{19}H_{28}O_7N_4$ requires C, 53·8; H, 6·6; N, 13·2 per cent).

[19] T. M. Reynolds and R. Robinson *J. Chem. Soc.* 594 (1934).

Acknowledgements—Grateful acknowledgement is made to the Colonial Products Council for supplies of plant material, to Messrs. T. and H. Smith, Ltd. (Edinburgh) for help with the extraction, and to Imperial Chemical Industries, Ltd. (Dyestuffs Division) for gifts of chemicals. Thanks are also due to Dr. G. Eglinton (University of Glasgow) for the infra-red measurements (carried out by Mr. F. Gisbey) and for help with their interpretation, to Sir Robert Robinson, O.M., F.R.S., for his continued interest in this work, and to Dr. W. Klyne for helpful discussion.

VOL.
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1957

Tetrahedron, 1957, Vol. 1, pp. 310–316. Pergamon Press Ltd., London

SYNTHESIS OF DIMETHYL THAMNOLATE AND DIMETHYL HYPOTHAMNOLATE

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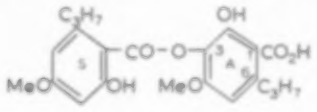
(*Received* 14 *May* 1957)

Abstract—Methyl 5-hydroxyhaematommate (XIX) and methyl 5-hydroxy-β-orcinolcarboxylate (XII) are conveniently made by the application of paranuclear oxidation using methyl haematommate and methyl β-orcinol carboxylate respectively. These undergo preferential acylation of the hydroxyl in the *meta* (5) position and by employing this property, syntheses of dimethyl thamnolate (XVIII) and dimethyl hypothamnolate (VII) have been accomplished.

IN an earlier paper[1] on the biogenesis of lichen depsides and depsidones, it was pointed out that *meta* depsides were invariably produced when the orcinol unit forming the right half (A of formula I) had undergone nuclear oxidation involving the 3 or the 5 position. Both types are known. Sekikaic acid (I), homosekikaic acid (II), ramalinolic adid (III) and boninic acid (IV) are examples of the first type, and the orcinol unit forming the A part provides a *meta* hydroxyl group in the 3 position. Thamnolic acid (V) and hypothamnolic acid (VI) belong to the second type, where the *meta* hydroxyl group is in the 5 position; the unit involved is a β-orcinol derivative and hence only the 5 position can undergo oxidation.



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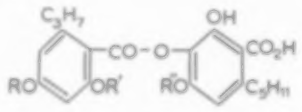
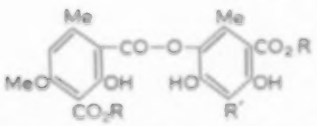


II, R=R″=OMe; R′=H
III, R=OMe; R′=R″=H
IV, R=R′=R″=OMe



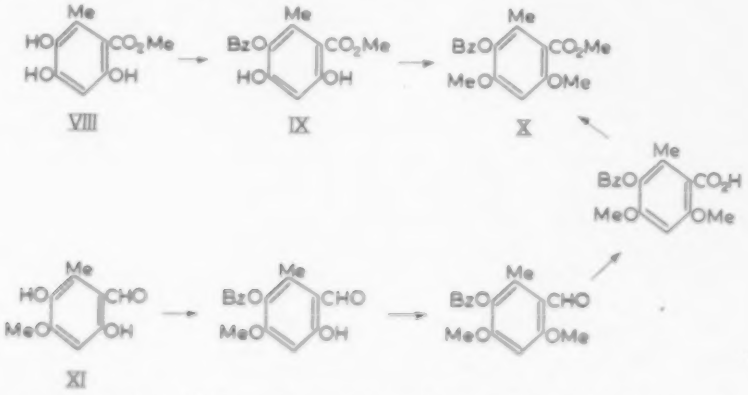
V, R=H; R′=CHO VI, R=H; R′=Me
VII, R=R′=Me XVIII, R=Me; R′=CHO

After a consideration of the reactivity of the concerned positions, the view was expressed that nuclear oxidation takes place in the C_8 (orsellinic) unit prior to the depside formation and since a *meta* hydroxyl group is thus rendered available, a *meta* depside results. It was definitely implied that a *meta* depside is more favoured as compared with a *para* depside and that it is formed directly from the C_8 components. The correctness of the above view was supported by the war-time publication, which came to our notice much later, describing the laboratory synthesis of ramalinolic acid (III)[2] and dimethyl hypothamnolate (VII),[3] in which use was made of the preferential *meta* acylation.

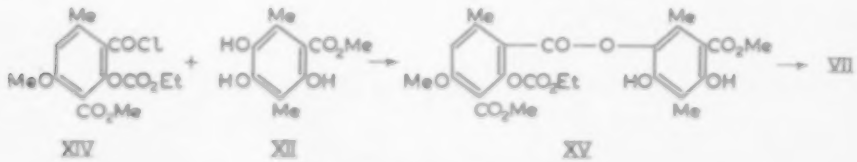
[1] T. R. Seshadri *Proc. Indian Acad. Sci.* A **19**, 1 (1944).
[2] Y. Asahina and T. Kusaka *Ber. Dtsch. Chem. Ges.* **69**, 1896 (1936).
[3] Y. Asahina, F. Fuzikawa and H. Aoki *Ber. Dtsch. Chem. Ges.* **74**, 824 (1941).

In continuation of our earlier paper on the role of nuclear oxidation in the biogenesis of lichen acids,[4] the synthesis of dimethyl hypothamnolate (VII) has now been re-examined with the result that considerable simplification has been effected. Further by these means, the synthesis of a more complex *meta* depside viz., thamnolic acid (V) as its dimethyl ester (XVIII) has also been accomplished.

In exploratory experiments, a simpler case studied was the monobenzoylation of methyl 5-hydroxyorsellinate (VIII). The product obtained contained the benzoyl group linked to the 5-hydroxyl group (IX), since on complete methylation, it yielded a dimethyl ether which agreed with methyl 2 : 4-dimethoxy-5-benzoyloxy-6-methylbenzoate (X) prepared earlier by Asahina and Kusaka[5] by a different and unambiguous route. They started from 2 : 5-dihydroxy-4-methoxy-6-methylbenzaldehyde (XI) and proceeded through the stages indicated below.

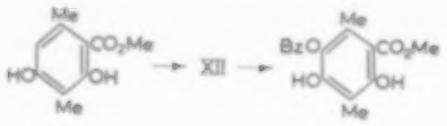


The next example studied was the mono-acylation of methyl 5-hydroxy-β-orcinolcarboxylate (XII). This compound has now been readily obtained by the nuclear oxidation of methyl β-orcinolcarboxylate (XIII) with alkaline potassium persulphate. The earlier synthesis of this compound was made starting from *p*-xyloquinone and passing through a large number of steps.[3] Condensation of (XII) with one mole of 2-ethylcarbonato-3-carbomethoxy-4-methoxy-6-methylbenzoyl chloride (XIV), prepared by the method of Asahina *et al.*,[3] gave the carboethoxy derivative of dimethyl hypothamnolate (XV), which on decarboethoxylation gave dimethyl hypothamnolate (VII).



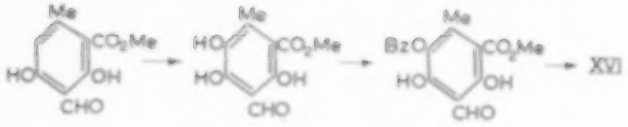
The monobenzoylation of methyl 5-hydroxy-β-orcinolcarboxylate (XII) has also been carried out and on the basis of the above analogy, the benzoyl group has been considered to be linked in the 5 position (XVI). This has been used later as a reference compound.

[4] K. Aghoramurthy and T. R. Seshadri *Proc. Indian Acad. Sci.* A 35, 327 (1952).
[5] Y. Asahina and T. Kusaka *Bull. Chem. Soc. Japan* 17, 158 (1942).



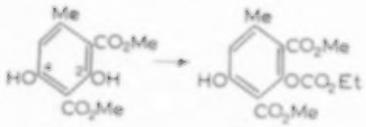
XIII XVI

For the synthesis of dimethyl thamnolate (XVIII), in which the part A contains an aldehydic group instead of the methyl group, two points had to be worked out: (i) the preparation of methyl 5-hydroxyhaematommate (XIX), and (ii) the depside condensation with this compound. The preparation of (XIX) has been achieved in a simple manner by the nuclear oxidation of methyl haematommate (XX).



XX XIX XXVI

Some difficulty was expected in the second step owing to the influence of the carbonyl of the aldehyde group, which in certain cases has been considered to activate the hydroxyl group in the 2 position over that in the 4 position. Thus, Asahina and Yanagita[6] and Asahina and Sakurai[7] have found that the monocarboethoxylation of dimethyl orcinol-2 : 4-dicarboxylate (XXI) yields the 2-carboethoxy derivative (XXII).



XXI XXII

Similarly, the monocarboethoxylation of methyl haematommate (XX) has been shown to yield the 2-monocarboethoxy derivative (XXIII).[7] The monobenzoylation of ethyl phloroglucinoldicarboxylate (XXIV) has also been reported to yield the 2-mono benzoyl derivative (XXV).

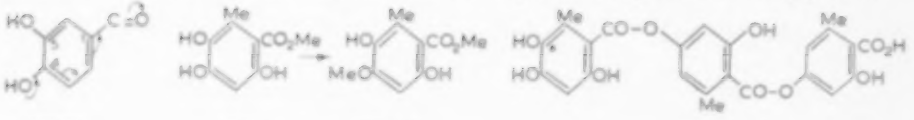
XX XXIII XXIV XXV

In order to make sure of the position of partial acylation, the monobenzoylation of methyl 5-hydroxyhaematommate (XIX) was first effected. The monobenzoyl derivative, when subjected to the Clemmensen reduction yielded a compound identical with the one obtained by the partial benzoylation of methyl 5-hydroxy-β-orcinolcarboxylate viz., (XVI). Hence, in the case of methyl 5-hydroxyhaematommate also, the benzoyl group should have entered the 5 position (XXVI), and the projected synthesis of

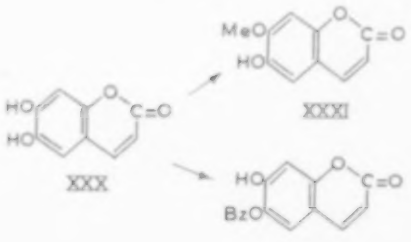
[6] Y. Asahina and M. Yanagita *Ber. Dtsch. Chem. Ges.* **66,** 393 (1933).
[7] Y. Asahina and Y. Sakurai *Ber. Dtsch. Chem. Ges.* **71,** 2561 (1938).

dimethyl thamnolate seemed to be feasible. Condensation of the acid chloride (XIV) with methyl 5-hydroxyhaematommate (XIX) yielded a carboethoxy derivative which on decarboethoxylation yielded dimethyl thamnolate (XVIII) identical in every respect with a specimen prepared by the controlled esterification of naturally occurring thamnolic acid (V) with diazomethane, according to the method of Asahina *et al.*[3]

Besides what has been mentioned above regarding the preferential formation and greater stability of *meta* depsides, may be mentioned the earlier work of Fischer and co-workers[9] on the formation of gallic acid *meta* depsides by the transformation of the *para* isomers. Recently, Critchlow, Haworth, and Pauson[10] observed a similar transformation in the case of 4-benzoylpyrogallolcarboxylic acid also. No satisfactory explanation seems to have been offered so far for the preferential formation of the *meta* depsides or for their greater stability. The following tentative explanation is now suggested. As a result of the electromeric polarisation initiated by the C=O group in the structure (XXVII), the hydroxyl group in the *para* (4) position will become more acidic whereas the one in the *meta* (5) position will be unaffected. Consequently an ester involving the *para* hydroxyl will have part of the instability of an anhydride, whereas the one involving the *meta* hydroxyl will be more akin to an ester and thus be more stable. The reactivity of these hydroxyl groups towards methylation supports the above views. A *para* hydroxyl group, being more acidic, should be methylated with greater ease, whereas the *meta* one should be less reactive. This is actually found to be the case, Thus methyl 5-hydroxyorsellinate (VIII) on partial methylation has now been found to give the 4-methyl ether (XXVIII). A similar case is hiascinic acid (XXIX). It has been reported that the *meta* hydroxyl group marked with an asterisk in (XXIX) is resistant to methylation.[5] The behaviour of aesculetin (XXX) towards partial methylation and partial benzoylation also follows a similar course. Partial methylation gives the 7-monomethyl ether[11] (XXXI) whereas partial benzoylation gives the 6-benzoyl derivative[12] (XXXII). In this case the influence of the C=O group is transmitted to the benzene ring through the ethylenic link present in conjugation.



XXVII VIII XXVIII XXIX



XXX XXXI XXXII

[5] H. Leuchs and I. Waldorf *Ann.* **460**, 1 (1928).
[9] E. Fischer, M. Bergmann and W. Lipschitz *Ber. Dtsch. Chem. Ges.* **51**, 45 (1918).
[10] A. Critchlow, R. D. Haworth and L. Pauson *J. Chem. Soc.* 1321 (1951).
[11] G. Bargellini and L. Monti *Gazzetta* **45**, 97 (1915).
[12] F. S. H. Head and A. Robertson *J. Chem. Soc.* 1266 (1939).

EXPERIMENTAL

Methyl 5-benzoyloxyorsellinate (IX)

A mixture of methyl 2 : 4 : 5-trihydroxy-6-methylbenzoate[4] (2 g), benzoyl chloride (1·4 cm³) and pyridine (2 cm³) in dry ether (100 cm³) was left at room temperature for 18 hr. The ether solution was washed successively with dilute hydrochloric acid, water, and saturated sodium hydrogen carbonate solution and dried. Evaporation of ether gave the *benzoate* as a solid which crystallised from methanol as colourless prisms and needles, m.p. 212–213° (2 g) (Found: C, 63·9; H, 4·6. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6 per cent). It produced a blue colour with ferric chloride and a yellow solution with aqueous sodium hydroxide.

Methyl 2 : 4-*dimethoxy*-5-*benzoyloxy*-6-*methylbenzoate* (X)

Methylation of the above ester with dimethyl sulphate by the acetone–potassium carbonate method for 12 hr gave the dimethyl ether, which crystallised from alcohol as rectangular tablets, m.p. 156–57°. It did not give any colour with ferric chloride or aqueous sodium hydroxide. Asahina and Kusaka[5] gave the same m.p.

Methyl 5-hydroxy-β-orcinolcarboxylate (XII)

A solution of methyl β-orcinolcarboxylate[13] (5 g) in aqueous sodium hydroxide (10 per cent; 40 cm³) was treated at 0° with stirring for 2 hr with aqueous potassium persulphate (6 per cent; 100 cm³); the mixture was kept at room temperature for 24 hr, acidified to Congo-red with concentrated hydrochloric acid, and extracted with ether (5 × 100 cm³). The ethereal extracts were dried and evaporated to yield the unchanged ester (1 g). The aqueous solution was treated with more concentrated hydrochloric acid (30 cm³) and sodium sulphite (2 g), heated at 80° for 1 hr, cooled, saturated with sodium chloride, and extracted with ether (5 × 200 cm³). The ether extracts were dried and evaporated and the solid residue was crystallised from ethyl acetate–light petroleum (40–60°). The *hydroxy ester* was obtained as colourless needles, m.p. 151–152°. Asahina *et al.* gave the same m.p. It gave a red-brown colour with ferric chloride and a purple colour with traces of alkali. The triacetate formed colourless needles from ethyl acetate–light petroleum (40–60°) m.p. 197–198°. Asahina *et al.* (*loc. cit*) gave the same m.p.

Dimethyl hypothamnolate (VII)

A mixture of 2-ethylcarbonato-3-carbomethoxy-4-methoxy-6-methylbenzoyl chloride[3] (0·55 g), methyl 5-hydroxy-β-orcinolcarboxylate (0·35 g) and pyridine (5 cm³) in dry ether (100 cm³) was left at room temperature for 20 hr. The ether solution was washed successively with dilute hydrochloric acid, water and saturated sodium hydrogen carbonate solution. The residue obtained on evaporation of the ether was dissolved in acetone (10 cm³), treated with N sodium hydroxide (20 cm³) and kept at room temperature in a hydrogen atmosphere for 1 hr. Acidification with dilute hydrochloric acid gave dimethyl hypothamnolate which crystallised from benzene as colourless prismatic needles, m.p. 200° (Found: C, 57·8; H, 5·3. Calc. for $C_{21}H_{22}O_{10}$, C, 58·1; H, 5·1 per cent). It gave a purple colour with ferric chloride and a purple

[13] W. B. Whalley *J. Chem. Soc.* 3278 (1949).

solution with alkalis. Asahina *et al.*[3] gave the m.p. 197–198° and reported similar colour reactions.

Methyl 5-benzoyloxy-β-orcinolcarboxylate (XVI)

The condensation of benzoyl chloride with methyl 5-hydroxy-β-orcinolcarboxylate was carried out as described previously using equimolar quantities of reactants. The *monobenzoate* crystallised from benzene as colourless needles, m.p. 176–177° (Found: C, 64·3; H, 5·2. $C_{17}H_{16}O_6$ requires, C, 64·6; H, 5·1 per cent). It gave a transient purple colour with ferric chloride and a purple solution with alkalis.

Methyl 5-hydroxyhaematommate (XIX)

The experimental procedure was similar to that described for methyl 5-hydroxy-β-orcinolcarboxylate. Methyl haematommate[14] (6 g) yielded unchanged material (1 g) and *methyl 5-hydroxyhaematommate* (1·5 g), yellow prisms (from ethyl acetate), m.p. 150–152° (Found: C, 53·7; H, 5·0. $C_{10}H_{10}O_6$ requires C, 53·1; H, 4·4 per cent). It gave an intense green colour with alcoholic ferric chloride and a yellow solution with alkalis.

Methyl 5-benzoyloxyhaematommate (XXVI)

The condensation of benzoyl chloride and methyl 5-hydroxyhaematommate was carried out using equimolar quantities as described before. The *benzoate* crystallised from alcohol as colourless flat needles, m.p. 152–154° (Found: C, 62·2; H, 4·5. $C_{17}H_{14}O_7$ requires, C, 61·8; H, 4·3 per cent). It gave wine-red colour with alcoholic ferric chloride and a yellow solution with alkalis.

Methyl 5-benzoyloxy-β-orcinolcarboxylate (XVI) *by Clemmensen Reduction*

To a mixture of the above benzoate (1 g) and zinc amalgam (20 g) in alcohol (25 cm³), was added dilute hydrochloric acid (2 : 1; 30 cm³), and the contents were refluxed for ½ hr. The amalgam was removed by filtration. The filtrate on cooling gave *methyl 5-benzoyloxy-β-orcinolcarboxylate* which crystallised from benzene as shiny thin needles, m.p. 176–177° alone or on admixture with the sample described previously.

Dimethyl thamnolate (XVIII)

The condensation of 2-ethylcarbonato-3-carbomethoxy-4-methoxy-6-methylbenzoyl chloride (0·75g) with methyl 5-hydroxyhaematommate (0·5 g) was carried out as described in the case of dimethyl hypothamnolate. Dimethyl thamnolate was obtained as colourless prisms from benzene–light petroleum, m.p. 160° (Found: C, 56·4; H, 4·9. Calc. for $C_{21}H_{20}O_{11}$, C, 56·3; H, 4·5 per cent). It gave a wine-red colour with ferric chloride and a yellow solution with alkalis. A mixed m.p. with an authentic specimen of dimethyl thamnolate, m.p. 158° prepared from thamnolic acid by esterification with diazomethane according to the method of Asahina *et al.*[3] showed no depression. The infra-red spectra in chloroform solution of the natural and synthetic specimens were identical in the 5–7 μ region.

Methyl 2:5-dihydroxy-4-methoxy-6-methylbenzoate (XXVIII)

A solution of methyl 5-hydroxyorsellinate (0·6 g; 1 mol.) and dimethyl sulphate (0·3 cm³; 1 mol.) in dry acetone (50 cm³) was refluxed with anhydrous potassium

[14] V. V. K. Sastri and T. R. Seshadri *Proc. Indian Acad. Sci.* A **12**, 502 (1940).

carbonate (2 g) for 12 hr. The acetone solution on evaporation yielded the methyl ether as a solid which crystallised from alcohol as colourless needles, m.p. 154°. A mixed m.p. with an authentic specimen of (XXVIII) described in an earlier paper[4] showed no depression. It gave a transient blue colour with ferric chloride which changed into green.

Acknowledgements—Our grateful thanks are due to Dr. C. A. Wachtmeister, and Prof. S. Shibata for a generous supply of thamnolic acid, and to Dr. B. D. Saxena of National Physical Laboratory of India for the infra-red spectra.

Tetrahedron, 1957, Vol. 1, pp. 317–327. Pergamon Press Ltd., London

TAUTOMERIC EQUILIBRIUM OF KETONIC AND *CIS*- AND *TRANS*-ENOLIC FORMS OF β-DICARBONYL COMPOUNDS IN SOLUTION*

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(*Received* 14 *May* 1957)

Abstract—In this paper the tautomeric equilibrium of ketonic and *cis*- and *trans*-enolic forms of β-dicarbonyl compounds is considered as an acid-base protolytic one. The application of the Brønsted–Izmaylov theory has enabled to suggest a general equation $K_{TS} = \delta\mathscr{L} + \delta_1$ for keto–enol equilibrium constants, depending on the solvent, the well known Meyer's equation being included in it as a particular case. Equilibrium constants have been bromometrically determined in a number of solvents of keto–enols of three types, i.e. "*cis*-fixed", "*trans*-fixed" and that involving both stereoisomeric forms. A method for quantitative determination of *cis*-*trans*-enol equilibrium had been proposed.

THE application to problems of tautomerism of the theory of protolytic acid-base equilibrium proposed by Brønsted[1,2] and recently further developed by Izmailov,[3,4,5] has been the subject of previous papers by the present authors[6–9] in which a quantitative interpretation of the ionic theory of tautomerism has been discussed.

This theory was first put forward by Wislicenus,[10] and in recent years Lapworth, Lowry, Ingold *et al.* and Baker[11–14] have studied the qualitative aspect of the theory starting from the concept of the formation of a "common ion" (by ionic dissociation of tautomeric forms) which is capable of recombination with oppositely charged ions at two points of the molecule.

Similar ideas were formulated by Arndt and Eistert,[15,16] who investigated the

$$pk_{AS_1} = pk_{AS_2} + \text{const.}$$

relation between the structure of keto-enols, acidity, solvation and enolisation. The

* Translated by A. L. Pumpiansky, Moscow.

[1] Y. N. Brønsted *Chem. Rev.* **5**, 291 (1928).
[2] Y. N. Brønsted *Z. Phys. Chem.* A **169**, 32 (1934).
[3] N. A. Izmailov *Zh. Phys. Khim. SSSR* **23**, 639, 643 (1949).
[4] N. A. Izmailov *Zh. Phys. Khim. SSSR* **24**, 321 (1950).
[5] N. A. Izmailov *Proceedings of the Kharkov University, U.S.S.R. Chemical Research Institute* Vol. 10, p. 5 (1953).
[6] M. I. Kabachnik *Dokl. Akad. Nauk. SSSR* **83**, 407, 859 (1952).
[7] M. I. Kabachnik and S. T. Yoffe *Dokl. Akad. Nauk. SSSR* **91**, 833 (1953).
[8] M. I. Kabachnik Problems of organic reaction mechanism. *Proceedings of the Kiev Conference held on* 2–5 *June*, 1952 p. 126. Kiev (1954).
[9] M. I. Kabachnik *Usp. Khim. SSSR* **25**, 138 (1956).
[10] W. Wislicenus Über Tautomeric. *Ahrenssammlung chem. u. chem. techn. Vorträge* **2**, 230 (1898).
[11] A. Lapworth and A. O. Hann *J. Chem. Soc.* **81**, 1512 (1902).
[12] T. Lowry *J. Chem. Soc.* 2557 (1927).
[13] C. Ingold, C. Shopee and J. F. Thorpe *J. Chem. Soc.* 1477 (1926).
[14] J. Baker *Tautomerism.* London (1934).
[15] F. Arndt, B. Eistert *Ber. Dtsch. Chem. Ges.* **74**, 423 (1941).
[16] F. Arndt, L. Loewe and R. Ginkök *Rev. Fac. Sci. univ. Istanbul* A **11**, 147 (1946)

relation between acidity and enolisation has proved to be of great importance to this problem, and in this connection the investigations of Schwarzenbach[17–20] should be mentioned.

We have based our investigation on the following concept. If the tautomeric equilibrium is an ionic one and consists in the transfer of a proton from one point of the molecule to another by proton transferring particles then, irrespective of the kinetics of this transfer, the conditions for tautomeric equilibrium should be determined by the equilibrium of the ketonic and enolic forms as acids with the corresponding ions, in the simplest case—with their common enolate—anion and solvated hydrogen ions. The tautomeric keto-enol equilibrium should then obey the laws of equilibrium exhibited by ordinary acids and bases. Experiments show this to be the case.

According to Pedersen,[21] keto-enol equilibrium can be represented as a triple buffer system:

$$KH + S \rightleftarrows E^- + HS^+ \rightleftarrows EH + S$$

(with *KH*-ketone, *EH*-enol, E^--enolate-anion, *S* and HS^+-solvent and respective cation). Tautomeric equilibrium constant can then be designated in terms of the acidity constants.

$$\frac{EH}{KH} = K_{TS} = \frac{k_{KS}}{k_{ES}} = \frac{k_K}{k_E} \cdot \frac{f_{KS}}{f_{ES}}.$$

where k_K and k_E are thermodynamic acidity constants of ketone and enol, f_{KS} and f_{ES} are the respective activity coefficients. The activities being referred to a standard common to all solvents, k_K and k_E do not depend on the medium. This relationship is a general one and is applicable to any prototropic ionic tautomeric system such as lactim-lactams, thione-thiols and others. The factor k_K/k_E denotes the enolisability of the keto-enol as such. It may be termed "the thermodynamic tautomeric equilibrium constant":

$$\frac{k_K}{k_E} = K^t = \frac{a_E}{a_K}$$

This factor shifts the equilibrium to the form with the smaller thermodynamic acidity constant. The factor f_{KS}/f_{ES} refers to the influence of solvation on the equilibrium ratio shifting it to the more solvated form. If the thermodynamic constant of the tautomeric equilibrium is either very large or small, the change in the factor f_{KS}/f_{ES} does not essentially effect the equilibrium ratio, which is shifted to one side practically in all media (α-pyridon,[22] carbostyril,[23] α-aminopyridine,[24] nitromethane[25] and others).

The effect of the solvent on the tautomeric equilibrium ratio can be represented in

[17] G. Schwarzenbach *et al.* *Helv. Chim. Acta* **23**, 1147, 1162 (1940).
[18] G. Schwarzenbach *et al.* *Ibid.* **27**, 1049, 1701 (1944).
[19] G. Schwarzenbach *et al.* *Ibid.* **30**, 656, 669 (1947).
[20] G. Schwarzenbach *et al.* *Ibid.* **34**, 1954 (1951).
[21] K. J. Pedersen *J. Phys. Chem.* **37**, 751 (1933).
[22] G. Gustafson *Suom Kemist* B **18**, 11 (1945).
[23] M. I. Kabachnik, S. T. Yoffe and Yu. N. Sheinker *Zh. Obschei Khim. SSSR* **26**, 2025 (1956).
[24] S. J. Angyal and C. L. Angyal *J. Chem. Soc.* 1461 (1952).
[25] D. Turnbull and S. Maron *J. Amer. Chem. Soc.* **65**, 212 (1943).

terms of the Brønsted equation[1,2] which gives the following linear relationship between the logarithms of the ionisation constants in two solvents, S_1 and S_2:

$$pk_{AS_1} = pk_{AS_2} + \text{const.}$$

This relationship with $tg\alpha = 1$ has been repeatedly checked experimentally. As formulated by Izmailov, the value of the constant C remains the same for acids of one chemical type such as carboxylic acids, phenols, sulphonic acids, etc. For ketones and enols being acids of different chemical types, two simultaneous equations are required:

$$pk_{KS_1} = pk_{KS_2} + \text{const.}_1$$

$$pk_{ES_1} = pk_{ES_2} + \text{const.}_2$$

Hence, tautomeric equilibrium constants in two solvents, S_1 and S_2 must also display a linear relationship:

$$p\mathrm{K}_{TS_1} = p\mathrm{K}_{TS_2} + C \qquad (1)$$

This relationship has been confirmed for a large number of keto-enols in various solvents. It is also of a general nature. Thus, for example, the linear relationship with $tg\alpha = 1$ is also observed for tautomeric equilibrium constants of acylaminopyridines and acylaminothiazoles.[26]

Meyer's empirical relation[27]

$$\mathrm{K}_{TS} = \mathscr{E}\mathscr{L}$$

can readily be deduced[6] from equation (1).

At the same time there are instances in the literature where Meyer's relation does not hold, such as ethyl formylphenylacetate in hydroxylic solvents, "the *trans*-fixed" enols of Eistert.[28] This for example, in the case of ethyl formylphenylacetate is due to the formation of hydrates or hemiacetals, and in other more general cases to steric peculiarities of the enolic structure. Accordance with and deviation from Meyer's equation depend in general on the stereoisomerism of enolic forms. The present investigation is devoted to the fundamental and experimental investigation of this point.

Bromometrical determination of the keto-enol equilibrium constant actually results in the sum of *cis*- and *trans*-enolic concentrations. The tautomeric equilibrium constant

$$\mathrm{K}_{TS} = \frac{[E_{cis}H] + [E_{trans}H]}{[KH]}$$

can be represented as the sum of constants:

$$\mathrm{K}_{TS} = \mathrm{K}_{(cis\text{-enol/ketone})s} + \mathrm{K}_{(trans\text{-enol/ketone})s}$$

Applying the Brønsted-Izmailov theory to the acid-base equilibrium under consideration, one has to bear in mind that the three forms, ketonic and *cis*- and *trans*-enolic refer to acids of different chemcial types and accordingly the relation between

[26] Yu. N. Sheinker *Dokl. Akad. Nauk. SSSR* **113**, 5 (1957).
[27] K. Meyer *Ber. Dtsch. Chem. Ges.* **47**, 826 (1914).
[28] B. Eistert and W. Reiss *Ber. Dtsch. chem. Ges.* **87**, 92, 108 (1954).

their ionisation constants in any two solvents should be represented respectively as:

$$\text{for ketone: } pk_{KS_1} = pk_{KS_2} + C'_1$$

$$\text{for } cis\text{-enol: } pk_{E_{cis}S_1} = pk_{E_{cis}S_2} + C'_2$$

$$\text{for } trans\text{-enol: } pk_{E_{trans}S_1} = pk_{E_{trans}S_2} + C'_3$$

Hence we have two equations:

$$pk_{(cis\text{-enol/ketone})S_1} = pk_{(cis\text{-enol/ketone})S_2} + C_1 \quad (2)$$

$$pk_{(trans\text{-enol/ketone})S_1} = pk_{(trans\text{-enol/ketone})S_2} + C_2 \quad (3)$$

Applying the same reasoning as used by one of use in deriving Meyer's equation for

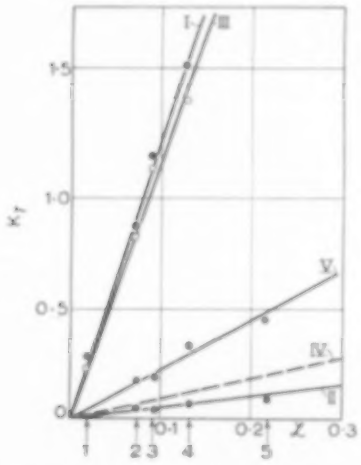


FIG. 1. The dependence of the tautomeric equilibrium constant on solvent used for "*cis*-fixed" and acyclic keto-enols.
I ethyl *cyclo*hexanonecarboxylate in 67 per cent methanol
II ethyl cyclopentanonecarboxylate in methanol.
III benzoylcamphor in chloroform.
IV ethyl acetoacetate in ethanol.
V ethyl benzoylacetate in benzene.

the equilibrium of two forms (ketonic and only one enolic),[6] we obtain two different equations

for keto-*cis*-enol equilibrium: $k_{(cis\text{-enol/ketone})S} = \mathscr{E}\mathscr{L}$

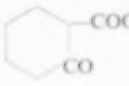
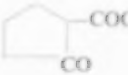
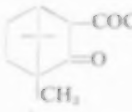
for keto-*trans*-enol equilibrium: $k_{(trans\text{-enol/ketone})S} = \mathscr{E}'\mathscr{L}'$

Hence, for overall keto-enol equilibrium

$$k_{TS} = \mathscr{E}\mathscr{L} + \mathscr{E}'\mathscr{L}'$$

This equation differs from that of Meyer by an additional term $\mathscr{E}'\mathscr{L}'$ referring to *trans*-enolisation. As in Meyer's relation, the value $\mathscr{E}$ refers to enolisability of the keto-enol to *cis*-enol, and $\mathscr{E}'$ to enolisability of the keto-enol to *trans*-enol. $\mathscr{L}$ and $\mathscr{L}'$ denote the enolising capacity of the solvent to *cis*- and, respectively, *trans*-enol. For each solvent, the values $\mathscr{L}$ and $\mathscr{L}'$ are equal to the equilibrium constants of two chosen keto-enols taken as standard for *cis*- and *trans*-enolisation. Constants $\mathscr{E}$ and

TABLE 1. ENOL CONTENT IN "*cis*-FIXED" AND ACYCLIC KETO-ENOLS (PER CENT)

Keto-enols	Solvents					
	67% CH_3OH	CH_3OH	$CHCl_3$	C_2H_5OH	C_6H_6	C_6H_{14}
$CH_3COCH_2COOC_2H_5$	2·0	7·1	8·7	11·4	18·3	54·3
	22·2	45·1	54·5	61·7	74·8	—
	2·0	4·0	3·7	5·9	8·2	—
$C_6H_5COCH_2COOC_2H_5$	(4·6)	(14·5)	(15·2)	(24·2)	(30·0)	(68·7)
	18·5	45·2	53·9	59·0	71·7	—

* G. A. Baluyeva (Private communication).

δ' do not depend on the solvent and are determined by the structure of the keto-enol, constants $\mathscr{L}$ and $\mathscr{L}'$ depending solely on the solvent and being common to all keto-enols.

To prove experimentally the suggested equation and to work out a method for determining the content of *cis*- and *trans*-enolic forms in solution it was necessary to choose standard keto-enols for *cis*- and, respectively, *trans*-enolisations.

Meyer is known to have applied as standard keto-enol ethyl acetoacetate. There were good reasons to believe enolisation of ethyl acetoacetate to be predominantly *cis*.[29,30] To prove this the equilibrium constants of ethyl acetoacetate in different solvents were compared with those cyclic β-keto-carboxylic esters, i.e., ethyl *cyclo*pentanone and ethyl *cyclo*hexanone-carboxylates. On purely structural grounds these substances can provide only *cis*-enolic forms, the *trans*- position being occupied by the ring. Such substances have been named by Eistert as "*cis*-fixed" enols. Determinations were carried out using Meyer's bromometrical back titration method[31] and directly, following Hesse and Krehbiel[32] with 1 per cent solution containing 0·06–0·08 mole/l., at 20°C. Data obtained are listed in Table 1 with some comparative literature values given in parentheses.

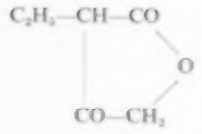
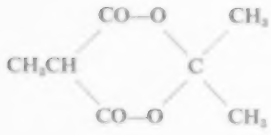
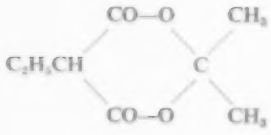
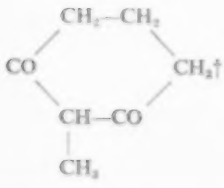
By plotting, as shown in Fig. 1, the ethyl acetoacetate equilibrium constant in different solvents (Meyer's $\mathscr{L}$ constant) against that of other keto-esters listed in the

[29] N. V. Sidgwick *J. Chem. Soc.* **127,** 907 (1925).
[30] P. Nachod *Z. Phys. Chem.* **A182,** 208 (1938).
[31] K. Meyer *Ber. Dtsch. Chem. Ges.* **45,** 2846 (1912).
[32] G. Hesse and G. Krehbiel *Liebigs Ann.* **593,** 35 (1955).

Table, it will be seen that the results obtained are in agreement with Meyer's original equation, all straight lines passing through the origin there being a satisfactory linear relationship. As two of the cited cyclic keto-enols lead only to "fixed" *cis*-enols and there also exists evidence about *cis*-enol being formed in benzoylcamphor, it may be concluded that, within the accuracy of the bromometrical method, it is possible to consider ethyl acetoacetate and ethyl benzoylacetate as substances forming only or almost exclusively *cis*-enols. This, of course, refers to all keto-enols which agree well with Meyer's formula.

Ethyl acetoacetate can this be retained as the standard substance for *cis*-enolisation. As standard substance for *trans*-enolisation any "*trans*-fixed" enol described by Eistert and Reiss can be used. These authors proposed as "*trans*-fixed" enols cyclic β-dicarbonyl compounds, which, for steric reasons can produce only *trans*-enolic forms. In the investigation mentioned above Eistert and Reiss found that the enol content of their compounds decreased from water to hexane being the converse of that found by Meyer. But, as the authors state, their bromometrical data were neither reproducible

TABLE 2. ENOL CONTENT IN "*trans*-FIXED" ENOLS (PER CENT)

Keto-enols	Solvents				
	67% CH_3OH	CH_3OH *	$CHCl_3$	C_2H_5OH	C_6H_6
	96·1	96·5	96·1	96·1	not dis.
	—	55·7	60·8	61·2	58·9
	—	71·5	73·5	73·3	70·8
	95·6	96·6	not dis.	93·8	not dis.

* The enol content in a polar solvent was determined by the authors from ultra-violet absorption spectra of methanol solutions acidified with HCl after exposure for 24 hr. Such conditions lead to enols producing methyl ethers, spectra of the latter being rather similar to those of enols.

† The sample has been kindly supplied by S. I. Zaviyalov.

nor exact owing to the rapid re-enolisation of bromo-ketones during the bromometrical determination. Their spectroscopic data is also doubtful.* We have therefore determined the enol content in various solvents of such "*trans*-fixed" enols, which do not undergo re-enolisation in the course of bromometrical determination. In Table 2

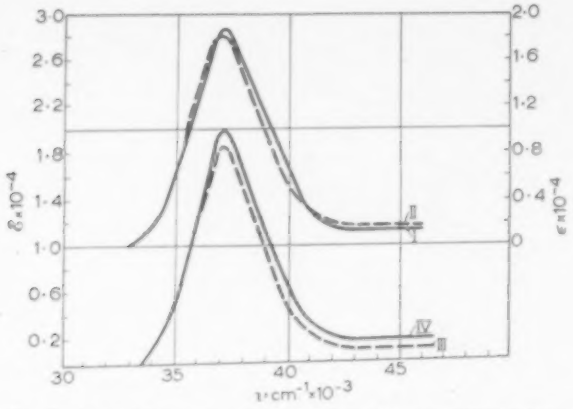


FIG. 2. Ultra-violet spectra of cyclic *iso*propylidene alkylmalonates.
I *iso*propylidene methylmalonate in methanol.
II *Idem* in ethanol.
III *iso*propylidene ethylmalonate in methanol.
IV *Idem* in ethanol.

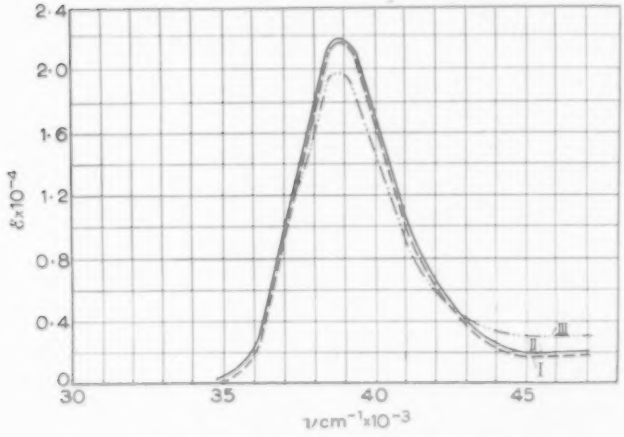


FIG. 3. Ultra-violet spectra of ethyltetronic acid
I in water
II in methanol.
III in ethanol.

the bromometrical data of the enol content are given for such keto-enols, using the direct method.

The consistency of tautomeric equilibrium constants of ethyl tetronic acid in water, methanol and ethanol and cyclic *iso*propylidene aklylmalonates in alcohols is substantiated by ultra-violet spectra (Figs. 2 and 3).*

* The spectra were supplied by the Optical laboratory of the Institute of Organo-element compounds, headed by I. V. Obreimov.

It follows from the data obtained that $\mathscr{L}'$ is independent of the solvent and the following equation can be derived for keto-enols.

$$K_{TS} = \mathscr{E}\mathscr{L} + \mathscr{E}_1 \qquad (4)$$

If the keto-enol produces only a *cis*-enolic form then $\mathscr{E}_1 = 0$ corresponding to the usual Meyer formula (linear relationship between K_{TS} and $\mathscr{L}$; the straight line passes through the origin). If only *trans*-enol is formed, then $\mathscr{E} = 0$ and the equilibrium constant does not depend on the type of solvent used. Finally, if in the tautomeric equilibrium both enolic forms are present together with the keto form, the relationship between K_{TS} and $\mathscr{L}$ must remain linear, but the straight line cuts on the axis Y an intercept $\mathscr{E}_1$. Having determined the keto-enol equilibrium constant in a number of solvents with a known $\mathscr{L}$, the *cis*-and *trans*-form ratio can be calculated.

This has been checked on keto-enols known to contain *cis*- and *trans*-enolic forms, such as α and γ-substituted acetoacetic esters, studied by Henecka.[33] Whilst α-methyl or α-ethyl substituted compounds readily form brightly coloured iron complexes, α-*iso*propyl derivatives as well as, according to our data, α-secondary butyl derivatives fail to react with ferric chloride or react very sluggishly. At the same time, as shown by bromometrical evidence, all these substances contain a definite amount of enol, enough for the coloured reaction to take place. The introduction of branched radicals into α-position and, to a somewhat smaller extent, into γ-position is thus seen to hinder the formation of the chelated salt. It is of importance to note, that this does not depend on the total enol content. In interpreting these results Henecka regards keto-enols that give no colour reaction with ferric chloride as *trans*-enols and it is necessary to conclude, that in these substances the formation of *cis*-enol with a planar six-ring hydrogen bonded cycle is hindered. Spectroscopic investigations carried out by Shigorin[34,35,36] substantiate that these α-alkylacetoacetic esters can only *trans*-enolise.

We have studied the effect of the solvent on the keto-enol equilibrium in several α-substituted esters of this series, the results obtained being listed in Table 3.

TABLE 3. ENOL CONTENT IN α-SUBSTITUTED ACETOACETIC ESTERS (PER CENT)

$CH_3COCHCOOC_2H_5$ (R)	67% CH_3OH	CH_3OH	C_2H_5OH	C_6H_6
R = C_2H_5	0·9	1·8	2·8	4·2
R *n*-C_3H_7	1·9	3·0	4·2	5·6
R *iso*-C_3H_7	2·6	3·0	3·1	3·6
R *n*-C_4H_9	3·4	4·3	5·4	6·2
R sec.-C_4H_9	10·5	10·6	10·6	10·8
R = H	2·0	7·1	11·4	18·3

[33] H. Henecka *Chemie der β-dicarbonylverbindungen* S. 122. Springer-Verlag (1950).
[34] D. N. Shigorin *Zh. Phys. Khim. SSSR* **23**, 505 (1949).
[35] D. N. Shigorin *Ibid.* **24**, 924, 932 (1950).
[36] D. N. Shigorin and A. P. Sholdinov *Ibid.* **24**, 954 (1950).

As seen from Fig. 4, by plotting $\mathscr{L}$ against K_{TS} the straight lines pass above the origin. The equilibrium of these keto-enols is thus represented by equation (4). From the data obtained one calculates the *cis*-enol content in the enolic fraction of the keto-enol.

$$\textit{cis}\text{-enol} = \frac{100\,\mathscr{E}\mathscr{L}}{\mathscr{E}\mathscr{L} + \mathscr{E}_1} \qquad \text{(per cent)}$$

the results calculated being given in Table 4.

One can also propose another way to calculate *cis-trans*-enolic equilibrium. One has first to determine the equilibrium constants for $k_{(cis\text{-enol}+trans\text{-enol/ketone})S}$ in two selected solvents for three groups of substances: (a) "*cis*-fixed" enols (b) "*trans*-fixed" enols and (c) keto-enols under investigation. Then one finds from the data for the

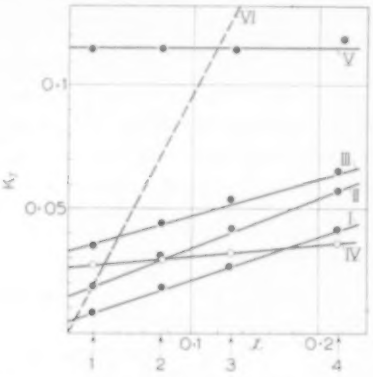


FIG. 4. The dependence of the tautomeric equilibrium constant on solvent used for α-substituted ethyl acetoacetates, $CH_3COCH{\cdot}COOC_2H_5 \rightleftharpoons CH_3COCHCOOC_2C_5$. I—R = C_2H_5, II—R = C_3H_7, III—R = C_4H_9, IV—R = *iso*-C_3H_7, V = secondary—C_4H_9, VI—R = H. Solvents: I. 67 per cent methanol; II. methanol; III. ethanol; IV. benzene.

two former groups the values of C_1 and C_2 constants in equations (2) and (3). Finally considering C_2 for "*trans*-fixed" enols to be 0, one calculates for the keto-enols in question the *cis*-to *trans*-from ratio as follows:

$$\frac{[E_{cis}H]_{S_1}}{[E_{trans}H]_{S_1}} = \frac{k_{TS_1} - k_{TS_2}}{k_{TS_2} - \alpha\, k_{TS_1}}$$

$$\frac{[E_{cis}H]_{S_2}}{[E_{trans}H]_{S_2}} = \frac{k_{TS_2} - k_{TS_1}}{k_{TS_1} - \frac{1}{\alpha}\, k_{TS_2}}$$

with $\alpha = 10^{+1}$. In Fig. 5 are plotted pK_{TS_1} against pK_{TS_1} for the keto-enols of the first group where $S_1 = 67$ per cent CH_3OH and $S_2 = C_6H_6$. Hence: $C_1 = 1{\cdot}0$ and $\alpha = 10$.

The results calculated using this method are to be found in parentheses in Table 4.

It will be seen, that the keto-enols which are sterically hindered do contain much of the *trans*-enolic form and the most hindered secondary butyl acetoacetate contains very little of the *cis*-form. As was to be expected the relative *cis-trans* ratio is strongly dependent on the solvent used.

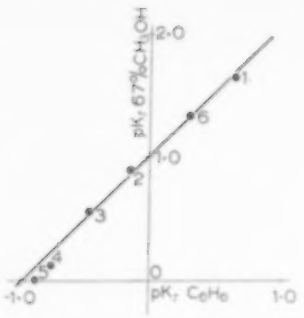


FIG. 5. The relationship between the tautometic equilibrium constants of "*cis*-fixed" and cyclic keto-enols in 67 per cent methanol and benzene.
1. ethyl acetoacetate.
2. ethyl 2-methyl*cyclo*hexanonecarboxylate.
3. ethyl *cyclo*hexanonecarboxylate.
4. acetylacetone (K. Meyer).
5. acetylacetone.
6. ethyl benzoylacetate.

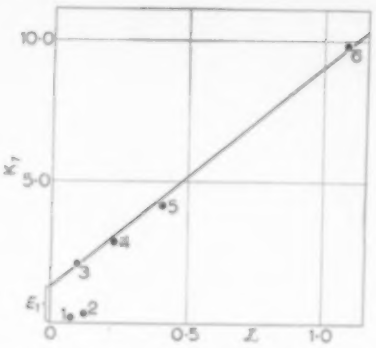


FIG. 6. The defendence of the tautomeric equilibrium constant of ethyl formylphenylacetate on the solvent used.
1. methanol.
2. ethanol.
3. chloroform.
4. benzene.
5. ether.
6. hexane.

TABLE 4. *Cis*-ENOL CONTENT IN THE ENOL FRACTION OF THE α-SUBSTITUTED ETHYL ACETOACETATES (PER CENT)

$CH_3COCHCOOC_2H_5$ (R = H)	$\mathscr{E}$	$\mathscr{E}_1$	Solvents			
			67% CH_3OH	CH_3OH	C_2H_5OH	C_6H_6
R = C_2H_5	0·177	0·005	46·6 (43·2)	74·8	83·1	89·5 (88·4)
R = *n*-C_3H_7	0·201	0·015	25·1 (23·4)	51·1	63·4	75·0 (75·0)
R = *iso*-C_3H_7	0·050	0·026	4·6 (4·1)	13·0	19·9	30·1 (30·1)
R = *n*-C_4H_9	0·156	0·033	10·6 (9·3)	26·9	37·9	51·5 (52·6)
R = sec.-C_4H_9	0·019	0·116	0·4 (0·4)	1·3	2·1	3·5 (3·7)

By making use of this method, we have also determined the *cis*-enol content in the enol fraction of ethyl formylphenylacetate in chloroform, benzene, ether and hexane. As seen from Fig. 6 there is in these solvents a linear relationship between K_{TS} and $\mathscr{E}$ (points 3, 4, 5 and 6). The intersect $\mathscr{E}_1$ is characteristic of the presence of the *trans*-form. Points 1 and 2 on the plot, referring to methanol and ethanol do not obey the general relationship, in agreement with findings of Wislicenus[37] that ethyl formylphenylacetate forms hemiacetals in alcoholic solutions.

In Table 5 are presented the values of total enol content and *cis*-enol content in the enol fraction.

[37] W. Wislicenus *Liebigs Ann.* **413**, 21 (1917).

TABLE 5. *Cis*-ENOL CONTENT IN THE ENOL FRACTION OF ETHYL FORMYLPHENYL ACETATE ($\mathscr{E} = 7{\cdot}253$, $\mathscr{E}_1 = 1{\cdot}208$) (PER CENT)

Solvent	Total enol content	*Cis*-enol content in the enol-fraction
Chloroform	66·4	35·3
Benzene	73·2	57·3
Ether	80·4	71·1
Hexane	90·8	87·7

CONCLUSIONS

(1) The principal regularities of the protolytic acid-base equilibrium have been shown to be applicable to the tautomeric equilibrium of a complex system, involving ketonic and *cis-trans*-enolic forms.

(2) A general equation $K_{TS} = \mathscr{E}\mathscr{L} + \mathscr{E}_1$ for the tautomeric ketonic-*cis-trans*-enolic equilibrium constant in different solvents has been derived, the well known Meyer's equation being included in it as a particular case.

(3) A method of quantitative determination of *cis*- and *trans*-enol content in solutions has been proposed and exemplified on α-substituted acetoacetates and ethyl formylphenylacetate.

Tetrahedron, 1957, Vol. 1, pp. 328–337. Pergamon Press Ltd., London

ALKALOID STUDIES—XIX*

ALKALOIDS OF SOME HAWAIIAN *RAUWOLFIA* SPECIES: THE STRUCTURE OF SANDWICINE AND ITS INTERCONVERSION WITH AJMALINE AND AJMALIDINE

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(*Received* 23 *July* 1957)

Abstract—The alkaloid composition of the following three Hawaiian *Rauwolfia* species—*R. sandwicensis* A.DC., *R. degeneri* Sherff and *R. mauiensis* Sherff—was determined. Aside from the known alkaloids serpentinine, ajmaline, tetraphylline and tetraphyllicine there were encountered trace amounts of two new dihydroindole alkaloids, mauiensine and sandwicensine as well as larger quantities of an isomer of ajmaline, which was named sandwicine ($C_{20}H_{24}N_2O_2$). Since sandwicine and ajmaline yield different dihydro derivatives which are convertible by lead tetra-acetate oxidation to a common indole hemi-acetal, sandwicine represents the C-17 epimer of ajmaline. Dihydrosandwicine was found to be identical with tetrahydroajmalidine, the sodium borohydride reduction product of ajmalidine, thereby proving that ajmalidine is 17-dehydroajmaline.

THE current interest in *Rauwolfia* alkaloids[1] has resulted in an examination of a large number of different *Rauwolfia* species. Our past work in this field has been limited to species indigenous to the American continent[2,3,4,5] in a search for alkaloids of unknown structure and it appeared of interest to study some Hawaiian species[6] of this genus. The chief reason was that the Hawaiian species are grouped in a separate section (*Ochrosioides*)[7] and it was conceivable that the alkaloid composition might differ from that of the other species.

The three species available to us were collected by one of the authors (P. J. S.) together with Dr. Harold St. John of the Botany Department of the University of Hawaii and were immediately processed by essentially the scheme developed by Hochstein *et al.*[8] for the separation of *Rauwolfia* alkaloids of different basicities.

* Paper XVIII in the Wayne series, W. B. Mors, O. R. Gottlieb and C. Djerassi *J. Amer. Chem. Soc.* **79**, 450 (1957).

† Post-doctorate research fellow at Wayne State University, 1956

‡ Lilly pre-doctorate research fellow at Wayne State University.

[1] A. Chatterjee, S. C. Pakrashi and G. Werner L. Zechmeister's *Progress in the Chemistry of Organic Natural Products* (Edited by Zechmeister). Vol. XIII, pp. 346–443. Springer Verlag, Vienna (1956).

[2] C. Djerassi, M. Gorman, A. L. Nussbaum and J. Reynoso *J. Amer. Chem. Soc.* **76**, 4463 (1954).

[3] C. Djerassi and J. Fishman *Chem. (Rev.) Ind.*, 627 (1955).

[4] S. C. Pakrashi, C. Djerassi, R. Wasicky and N. Neuss *J. Amer. Chem. Soc.* **77**, 6687 (1955).

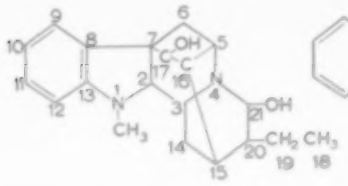
[5] W. B. Mors, P. Zaltzman, J. J. Beereboom, S. C. Pakrashi and C. Djerassi *Chem. (Rev.) Ind.*, 173 (1956).

[6] E. E. Sherff *A Preliminary Study of Hawaiian Species of the Genus Rauwolfia* Vol. 23, No. 7. Botanical Series, Field Museum of Natural History (1947).

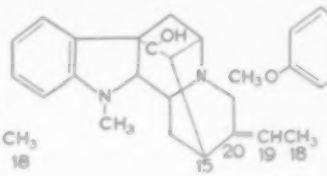
[7] R. E. Woodson, H. W. Youngken, E. Schlittler and J. A. Schneider *Rauwolfia* Chapter I. Little, Brown & Co., Boston (1957).

[8] F. A. Hochstein, K. Murai and W. H. Boegemann *J. Amer. Chem. Soc.* **77**, 3551 (1955).

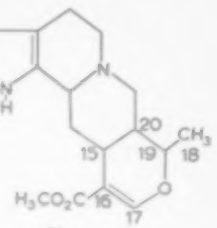
Rauwolfia degeneri Sherff[6] roots, collected on the Island of Oahu, yielded four known alkaloids—ajmaline (I),*[9,10] tetraphyllicine (II),[11] tetraphylline (III)[11] and serpentinine[11,12]—and it is striking to note that the same alkaloids were also encountered in the West Indian *Rauwolfia tetraphylla* L.[11] The co-occurrence of these four alkaloids is of definite biogenetic significance since it has already been pointed out[13] that a precursor of tetraphyllicine (II) is probably responsible for the origin of the



I



II



III

heterocyclic *E* ring of alkaloids of the tetraphylline (III) type as is already implied by the numbering system employed in the structural formulae.

A similar examination of *Rauwolfia sandwicensis* A.DC.[6] furnished tetraphylline (III), serpentinine, sandwicine (see below), a trace quantity of an impure dihydroindole alkaloid, which may have been tetraphyllicine (II) since the infrared spectra were virtually identical, and a small amount of a new dihydroindole alkaloid ("sandwicensine"), m.p. 260–262°, $[\alpha]_D + 56°$ (methanol), whose analysis was most compatible with $C_{19}H_{22}N_2O.CH_3OH$.

From *R. mauiensis* Sherff[6] there were isolated tetraphyllicine (II), serpentinine, sandwicine (see below) and a trace of a crystalline alkaloid ("mauiensine"), m.p. 240–242°, $[\alpha]_D + 184°$ (methanol), which appeared to correspond by analysis to $C_{20}H_{26}N_2O$. Unfortunately, sufficient amounts of sandwicensine and mauiensine could not be secured for further work but the ultraviolet and infrared data as well as the positive rotations clearly indicate that these substances should be assigned to the ajmaline group of alkaloids.

The principal alkaloid of *R. sandwicensis* and *R. mauiensis* was gelatinous and could not be induced to crystallize even after repeated purification by chromatography and countercurrent distribution. Its empirical formula corresponded to that of ajmaline ($C_{20}H_{26}N_2O_2$) and this was confirmed by analytical determinations on the crystalline dihydrochloride and dihydroiodide salts. The ultraviolet absorption spectrum was typical of a dihydroindole alkaloid and the infrared spectrum (Fig. 1) showed considerable similarities to that of ajmaline (I) which is also reproduced in Fig. 1 for comparison. Functional group analysis indicated the presence of one

* We are using a numbering system in the ajmaline series which is based on the hypothetical biogenetic precursor (see ref. 11) and the yohimbine numbering.

[9] R. B. Woodward *Angew. Chem.* **68**, 13 (1956); R. Robinson *Festschrift Arthur Stoll* pp. 457–467. Birkhauser, Basel (1957).

[10] R. B. Woodward, R. Robinson *et al.* *Tetrahedron.* To be published.

[11] C. Djerassi, J. Fishman, M. Gorman, J. P. Kutney and S. C. Pakrashi *J. Amer. Chem. Soc.* **79**, 1217 (1957).

[12] E. Schlittler, H. U. Huber, F. E. Bader and H. Zahnd *Helv. Chim. Acta* **37**, 1912 (1954).

[13] C. Djerassi, M. Gorman, S. C. Pakrashi and R. B. Woodward *J. Amer. Chem. Soc.* **78**, 1259 (1956).

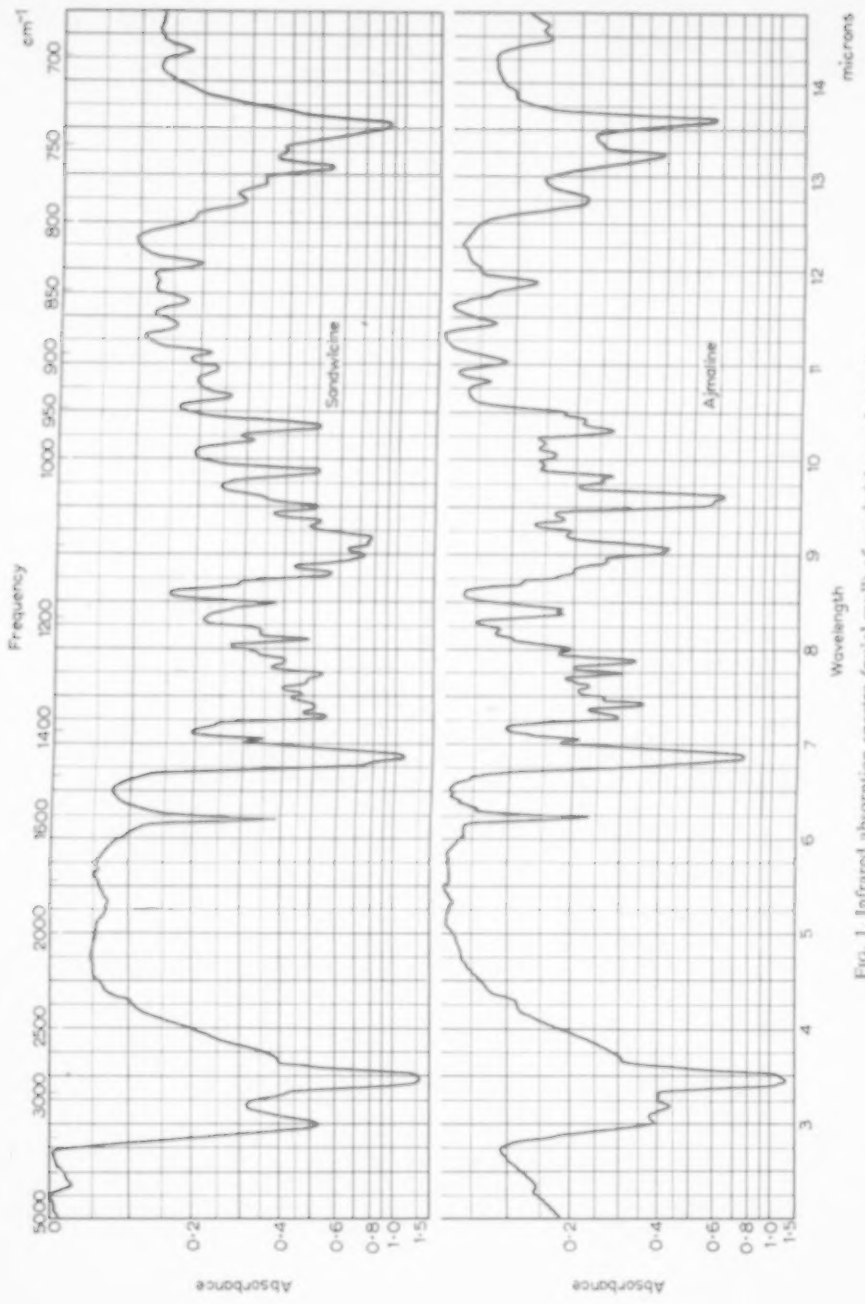


FIG. 1. Infrared absorption spectra (nujol mull) of sandwicine and ajmaline.

C-methyl and one N-methyl group and the absence of methoxyl functions. The basicity of sandwicine (pK_a' 8·5) is the same as that of ajmaline and its rotation is strongly positive (Table 1) as is that of ajmaline and related alkaloids, in contrast to that of most other *Rauwolfia* alkaloid types.

TABLE 1. MOLECULAR ROTATIONS IN THE SANDWICINE AND AJMALINE SERIES

Substance	$[\alpha]_D$	Solvent	$[M]_D$	$\Delta[M]_D$*
Ajmaline	+144°	$CHCl_3$	470	
*iso*Ajmaline	+72°	$CHCl_3$	242	−238
Dihydroajmaline	+54°	$CHCl_3$	179	−291
Ajmaline dihydroiodide	+72°	CH_3OH	417	
*iso*Ajmaline dihydroiodide	+64°	CH_3OH	373	−44
Sandwicine	+171°	CH_3OH		
	+180°	$CHCl_3$	592	
*iso*Sandwicine	+99°	$CHCl_3$	322	−270
Dihydrosandwicine	+102°	$CHCl_3$	336	−256
	+103°	CH_3OH		
Sandwicine dihydroiodide	+84°	CH_3OH	490	
*iso*Sandwicine dihydroiodide	+74°	CH_3OH	431	−59

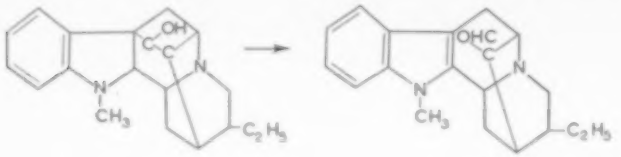
*$\Delta[M]_D = [M]_D$ (alkaloid) − $[M]_D$ (corresponding derivative).

The presence of at least one hydroxyl group in sandwicine was demonstrated by acetylation to an amorphous acetate, which exhibited infrared bands at 5·78 and 8·1 μ typical of alcoholic acetates. Quantitative microhydrogenation with a platinum oxide catalyst resulted—just as with ajmaline—in the uptake of 3 moles of hydrogen, thus excluding the presence of an ethylidene function as is found in tetraphyllicine (II).[11,13]

The above data strongly suggest a close structural similarity to ajmaline and this could be supported further by the following reactions. The presence of a carbinol amine moiety (as in ajmaline (I)) was shown by the fact that sandwicine could be reduced with sodium borohydride[14] to crystalline dihydrosandwicine ($C_{20}H_{28}N_2O_2$), the shift in molecular rotation (Table 1) being of the same order as observed in the ajmaline → dihydroajmaline transformation.[15] Furthermore, when sandwicine was boiled with methanolic potassium hydroxide, it was transformed into an isomer—*iso*sandwicine—with identical ultraviolet, but slightly different infrared spectrum. The very considerable change in the rotation, however, was again comparable (Table 1) to that observed in the ajmaline → *iso*ajmaline reaction[16] which is known to involve simply epimerization at C-20.

The spectroscopic and chemical data cited so far present unequivocal evidence for the presence of an N-methyldihydroindole nucleus as well as a structural unit encompassed by C-18, 19, 20, 21 and N-4 of ajmaline (I). The most cogent experiment for the attachment of the hydroxyl bearing C-17 carbon atom of ajmaline (I) to the β-position (C-7) of the dihydroindole nucleus is the lead tetra-acetate oxidation[9,10] of desoxyajmaline (IV) to the aldehyde (V) which now contains an indole ring.

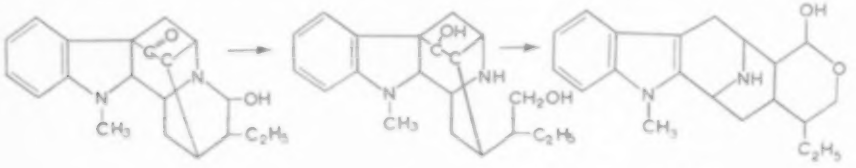
[14] S. Bose *J. Indian Chem. Soc.* **32**, 450 (1955).
[15] R. Robinson *Chem. (Rev.) Ind.*, 285 (1955).
[16] F. A. L. Anet, D. Chakravarti, R. Robinson and E. Schlittler *J. Chem. Soc.* 1242 (1954).



IV V

It was not possible to prepare the requisite desoxysandwicine since the conditions of the Robinson desoxyajmaline synthesis[15]—pyrolysis of dihydroajmaline hydrobromide—proved too strenuous when applied to dihydrosandwicine hydrobromide, the substance decomposing before reaching the desired temperature. Lead tetraacetate oxidation of ajmaline itself leads to a mixture, probably due to concurrent attack of the carbinol amine system, but it has been shown[10,*] that dihydroajmaline (VI) readily undergoes this reaction to yield an indolic hydroxy aldehyde (similar to V) which spontaneously cyclizes to the hemi-acetal (VII). When this oxidation was carried out with dihydrosandwicine, the identical hemiacetal (VII) (Fig. 2) was obtained as evidenced by mixture melting point determination as well as comparison of the infrared and ultraviolet absorption spectra, X-ray diffraction patterns and rotations. It is pertinent to note that the rotation shifts on oxidation from a positive value typical of the *Rauwolfia* dihydroindole alkaloids to a negative value characteristic of the *Rauwolfia* indole alkaloids. Since the only asymmetric center involved in the above oxidation is C-17, dihydroajmaline and dihydrosandwicine differ only at C-17. Sandwicine can, therefore, be named 17-epiajmaline although it is appreciated that isomerism at C-21 has not been excluded rigorously.

Dihydrosandwicine (VI) proved to be identical with tetrahydroajmalidine which was obtained† by sodium borohydride reduction of ajmalidine (VIII).[4] This



VIII VI VII

establishes the skeletal structure of ajmalidine as 17-dehydroajmaline (VIII) as had been proposed earlier[11,13] on circumstantial evidence.

EXPERIMENTAL‡

Isolation of alkaloids from Rauwolfia sandwicensis A.DC. The oven dried (44°) roots§ (1098 g) were ground in a Wiley mill to pass a 1 mm screen and extracted by

* We are greatly indebted to Prof. R. B. Woodward of Harvard University for providing us with excellent experimental details prior to publication.

† This experiment was performed by Dr. S. C. Pakrashi at Wayne State University.

‡ Melting points were determined on the Kofler block. The infrared and ultraviolet absorption spectra were determined in part by Mrs. Dolores Phillips (Wayne State University) and in part by the Physical Chemical Dept. of Eli Lilly & Co. We are indebted to the Lilly microanalytical group (B. Brown, G. M. Maciak, C. Hunter and G. Beckmann) for all microanalyses and to the Lilly Analytical Department for the optical rotations.

§ The root material (2200 g) was collected at 1600 ft altitude in the Kalanoo–North Halawa area, Koolau Mountains, Island of Oahu, and the botanical identification was carried out by Dr. Harold St. John.

heating under reflux three times for 18 hr each, with methanol. The combined methanolic extracts were evaporated *in vacuo* to yield 95 g of brown solid. This residue was dissolved in 700 cm³ of methanol, and 200 cm³ of glacial acetic acid, followed by 1100 cm³ of water, were added. Filtration through Celite and thorough extraction with hexane removed non-alkaloidal contaminants. The aqueous acid

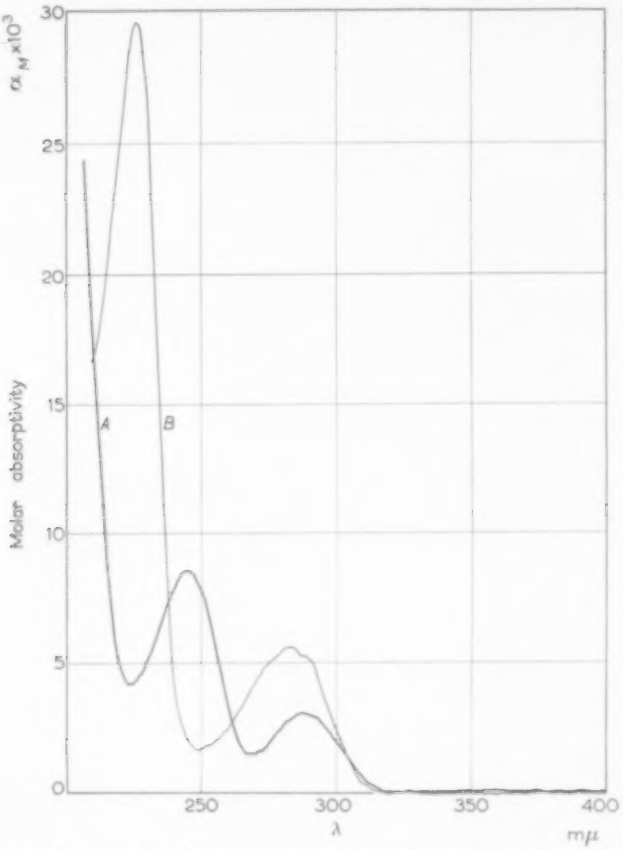


FIG. 2. Ultraviolet absorption spectra of dihydrosandwicine (VI) and (VII).
A—dihydrosandwicine
B—$Pb(OAc)_4$ oxidation product

solution was extracted with twelve 300 cm³ portions of benzene followed by chloroform and these extracts—containing the weakly basic alkaloids—were washed separately with 5 per cent ammonium hydroxide, dried and evaporated to yield respectively 6·0 g (benzene) and 8·0 g (chloroform) of solids.

The acidic solution was cooled in ice, ammonium hydroxide was added until pH 7 was reached and the medium strength bases (11·9 g) were extracted with chloroform. Finally the aqueous layer was made strongly alkaline (pH 11) with sodium hydroxide and extracted with chloroform to afford 6·0 g of strong bases.

Chromatography of the benzene-soluble acetate fraction on alumina did not provide any crystalline material. The chloroform-soluble acetates upon crystallization gave colorless crystals (0·04 per cent based on dry root) with a double m.p. 125° and

220–222°. These were identified as *tetraphylline* (III)[11] by mixture melting point determination as well as comparison of the X-ray diffraction patterns and infrared and ultraviolet spectra with those of an authentic specimen. Chromatography of the mother liquors on alumina led only to oils.

The medium strength bases, isolated at pH 7, were dissolved in benzene–chloroform (1 : 1) and chromatographed on 700 g of alumina which had been deactivated by the addition of 21 cm^3 of 10 per cent aqueous acetic acid. Elution with the same solvent mixture yielded 12 mg of colorless crystals, m.p. 269–272°, raised to 274–275° upon further recrystallization. The ultraviolet absorption spectrum (λ_{max}^{EtOH} 248 and 292 mμ, log ε 4·01 and 3·58) was typical of a dihydroindole and the infrared spectrum (KBr pellet) was virtually identical with that of *tetraphyllicine* (II). Further purification was precluded by lack of material but it is likely that this substance was impure tetraphyllicine. *Anal.* Calcd. for $C_{20}H_{24}N_2O$: C, 77·88; H, 7·84. Found: C, 77·19; H, 8·11.

Further elution with benzene–chloroform (1 : 3) yielded 40 mg of *sandwicencine*, m.p. 253–257°. The analytical sample was obtained from methanol whereupon it exhibited m.p. 260–262°, $[\alpha]_D$ + 56° (CH_3OH), λ_{max}^{EtOH} 246 and 290 mμ, log ε 3·82 and 3·35. The infrared spectrum (nujol mull) was similar but not identical with that of *iso*ajmaline[18] (m.p. 264–265°) and the mixture melting point was depressed by over 6°. No material was available for further work or duplicate analyses. *Anal.* Calcd. for $C_{19}H_{22}N_2O.CH_3OH$: C, 73·59; H, 8·03; N, 8·58; O, 9·80; methoxyl, 9·50. Found: C, 73·35; H, 8·27; N, 8·94; O, 9·76; methoxyl, 9·25; after redrying at 90° *in vacuo*, 0·73.

Further elution of this chromatogram with chloroform–methanol (99 : 1) afforded 1·0 g of *sandwicine*, the purification of which is discussed below.

The strongly basic alkaloid fraction was chromatographed on 400 g of deactivated alumina and elution with chloroform–methanol (99 : 1) yielded 50 mg of yellow solid, melting partially at 152–155° and the remainder near 260°. Recrystallization from methanol afforded *serpentinine*, m.p. 265–270° (dec.) identified by infrared, ultraviolet and X-ray comparisons with an authentic sample. The mother liquor material could not be crystallized but the infrared spectrum strongly indicated that it consisted chiefly of serpentine.

Isolation of alkaloids from Rauwolfia mauiensis Sherff. From 422 g of root material* there was obtained 249 g of dried powder and 25 g of methanol extract. When processed in the manner outlined above there was encountered (a) 0·15 g of benzene-soluble acetates, (b) 0·60 g of chloroform-soluble acetates, (c) 6·03 g of medium bases (pH 7 extractable) and (d) 0·10 g of strong bases. Chromatography of fractions (a), (b) and (d) did not yield any crystalline material.

The pH 7 bases were chromatographed on 400 g of acetic acid-deactivated alumina. Elution with benzene–chloroform (1 : 1) gave 30 mg of *mauiensine*, m.p. 235–240°, raised to 240–242° after recrystallization from acetone, $[\alpha]_{589}$ + 184°, $[\alpha]_{325}$ + 1038° (CH_3OH),† λ_{max}^{EtOH} 249 and 291 mμ, log ε 3·92 and 3·35. The infrared spectrum was typical of the ajmaline group of alkaloids and exhibited a characteristic band at 6·13 μ in a potassium pellet. Sufficient material for only one analysis was

* Collected by Dr. Harold St. John in the Hana district of East Maui near Kanaio at 1900 ft elevation in barren lava.

† Measured on a Rudolph spectropolarimeter with a xenon lamp.

available. *Anal.* Calcd. for $C_{20}H_{26}N_2O$: C, 77·38; H, 8·44; N, 9·03; N—CH_3, 4·84. Found: C, 77·16; H, 8·04; N, 8·59; N—CH_3, 6·58.

Additional elution with the same solvent pair furnished 11 mg of *tetraphyllicine*, m.p. 305–306° after recrystallization from acetone, and identified by direct comparison with an authentic specimen.[11]

Further development of the chromatogram with chloroform and chloroform–methanol (99 : 1) yielded 0·78 g of sandwicine containing a bright yellow impurity. This crude product was subjected to a seven stage countercurrent distribution with each funnel containing 50 cm³ each of chloroform (stationary phase) and citrate-phosphate buffer of pH 6·75. Combination of the contents of the first two funnels and crystallization from methanol gave 25 mg of *serpentinine*, m.p. 265–270° (dec.), identified with an authentic specimen. From the center funnels, 0·43 g of colorless *sandwicine* (see below) was obtained.

Isolation of alkaloids from Rauwolfia degeneri Sherff. Methanol extraction of 6350 g of fresh roots* (2550 g after drying) gave 319 g of methanol extract which was divided into 50 g of weak bases, 60 g of medium strength bases and 8 g of strong bases. Chromatography of the medium bases in the above described manner afforded in order of increasing polarity 45 mg of *tetraphyllicine* (II), m.p. 308–310°, 255 mg of *tetraphylline* (III)† m.p. 223–225°, 0·96 g of *serpentinine*, m.p. 260° (dec.) and 0·60 g of *ajmaline* (I), m.p. 158°. Identity was established in each instance by mixture melting point determination and infrared comparison with authentic samples.

Sandwicine. The alkaloid was obtained in a gelatinous form from both *R. sandwicensis* and *R. mauiensis* and could not be crystallized. It was best purified by dissolving in acetone and precipitating from a hot solution by the gradual addition of hexane. Countercurrent distribution (24 tubes) between chloroform and citrate-phosphate buffer (pH 6·73) on a sample of sandwicine from *R. sandwicensis* yielded—just as described above for *R. mauiensis*—a small amount of serpentinine from tubes 1 and 2. The contents of tubes 12–20 were pooled and redistributed into 24 fractions using the same system but no additional separation was encountered and the alkaloid behaved like a single entity with the following solvent systems in paper chromatograms: (a) *n*-butanol–water–acetic acid (4 : 5 : 1); (b) ethyl acetate–pyridine–water (7 : 2 : 1); (c) ethyl methyl ketone—1 per cent methanol saturated with water; (d) benzene–formamide. Sandwicine was identified by spraying with *p*-dimethylaminobenzaldehyde (blue color developing slowly on heating) or Dragendorff's reagent. The amorphous alkaloid exhibited $[\alpha] + 171°$ (CH_3OH), $+ 180°$ ($CHCl_3$) and its ultraviolet (λ_{max}^{EtOH} 246 and 292 mμ, log ε 3·91 and 3·46) absorption spectrum was typical of a dihydroindole. The infrared spectra (nujol mull) of sandwicine and ajmaline (I) are reproduced in Fig. 1. *Anal.* Calcd. for $C_{20}H_{26}N_2O_2$: C, 73·59; H, 8·03; N, 8·58; O, 9·80; C—CH_3, 4·60; mol. wt. 326. Found: C, 72·87; H, 8·22; N, 9·08; O, 10·54; C—CH_3, 3·48; mol. wt. (potentiometric titration), 322; p*K'a* (66 per cent DMF), 8·5.

Acetylation of sandwicine with acetic anhydride–pyridine (24 hr at 25°) yielded an amorphous acetate with strong infrared alcoholic acetate absorption ($\lambda_{max}^{CHCl_3}$ 5·78 and 8·1 μ).

* Collected on the ridge east of the central Makaleha valley, Mokuleia, Waianae Mountains, Island of Oahu, 1400 ft elevation. The two trees from which the roots were taken were identified by Dr. Harold St. John.

† An additional 1·0 g of tetraphylline was secured from the weakly basic fraction.

Sandwicine dihydroiodide was prepared by dissolving 50 mg of sandwicine in 10 cm³ of boiling acetone and adding 1 cm³ of 48 per cent hydroiodic acid. Crystallization commenced immediately and after concentrating to one-half the original volume, the solution was chilled and the crystals collected. The analytical sample was obtained by recrystallization from acetone or from methanol–hydroiodic acid, m.p. 238–240°, $[\alpha]_D$ + 84° (CH_3OH), pK_a' 8.5 (66 per cent dimethyl formamide, initial pH 2·65). The infrared and ultraviolet spectra were typical of dihydroindole salts. Sandwicine dihydroiodide could be prepared directly from the medium base fraction by treatment with acetone–hydroiodic acid.

Anal. Calcd. for $C_{20}H_{28}O_2I_2N_2$: C, 41·25; H, 4·85; N, 4·81; I, 43·58; mol. wt., 582. Found: C, 41·30; H, 5·00; N, 4·44; I, 43·36; mol. wt., 610 (potentiometric titration).

Sandwicine dihydrochloride was prepared in exactly the same fashion in acetone–concentrated hydrochloric acid, m.p. 210–213°, $[\alpha]_D$ + 129° (CH_3OH). *Anal.* Calcd. for $C_{20}H_{28}Cl_2N_2O_2$: C, 60·15; H, 7·07; Cl, 17·75; N, 7·01; O, 8·01; N—CH_3, 3·75. Found: C, 59·66; H, 7·16; Cl, 17·45; N, 6·92; O, 7·81; N—CH_3, 4·22.

Dihydrosandwicine. A solution of 0·3 g of sandwicine in 20 cm³ of ethanol was mixed with 0·5 g of sodium borohydride in 10 cm³ of 60 per cent ethanol and the solution was allowed to stand overnight before evaporating to dryness. Saturated sodium sulfate solution (25 cm³) containing 1 cm³ of concentrated ammonia was added and the resulting precipitate was extracted with chloroform. Evaporation of the chloroform solution yielded 0·24 g of crystalline dihydrosandwicine which was recrystallized from acetone giving long, coarse hexagonal rods, m.p. 210–212°, $[\alpha]_D$ + 102° ($CHCl_3$), λ_{max}^{EtOH} 246 and 288 mμ, log ε 3·90 and 3·45 (Fig. 2), λ_{max}^{nujol} 6·20 μ. *Anal.* Calcd. for $C_{20}H_{28}N_2O_2$: C, 73·13; H, 8·59; N, 8·53; mol. wt., 328·4. Found: C, 72·91; H, 8·85; N, 8·55; mol. wt. (X-ray), 327 (determined by Miss Ann Van Camp, Eli Lilly & Co.).

The hydrobromide salt (m.p. 250–255°) was prepared in the usual manner but it decomposed during attempted pyrolysis[17] to desoxysandwicine.

iso*Sandwicine.* When 0·15 g of sandwicine was heated under reflux for 8 hr with 0·3 g of potassium hydroxide and 25 cm³ of methanol, there was obtained 0·12 g of an amorphous powder, $[\alpha]_D$ + 99° ($CHCl_3$). The ultraviolet absorption spectrum was superimposable upon that of sandwicine, but the infrared spectra measured in chloroform (1 mm path), mineral oil mull or pyridine showed minor differences in the finger print region. The *dihydroiodide*, m.p. 242–245°, $[\alpha]_D$ + 74° (CH_3OH) was prepared as described above for sandwicine, and its infrared spectrum (nujol mull) proved to be different from that of sandwicine dihydroiodide. *Anal.* Calcd. for $C_{20}H_{28}I_2N_2O_2$: C, 41·25; H, 4·85. Found: C, 40·53; H, 4·89.

Lead tetra-acetate oxidation of dihydrosandwicine. A solution of 25 mg of dihydrosandwicine in 1 cm³ of acetic acid was treated for 15 sec with 40 mg of lead tetra-acetate dissolved in 5 cm³ of acetic acid. Hydrogen sulfide was passed into the solution, the lead sulfide was removed by filtration through Celite and the filtrate was evaporated to dryness *in vacuo*. Addition of water followed by decolorization with Norit, basification with ammonium hydroxide, extraction with chloroform, evaporation and recrystallization from benzene–methylene chloride furnished 20 mg of the hemi-acetal (VII). Its physical constants, m.p. 215–217°, $[\alpha]_D$—32° (chloroform), λ_{max}^{MeOH} 226 and 283 mμ, log ε 4·46 and 3·80 (Fig. 2), $\lambda_{max}^{CHCl_3}$ 3 2·75 (NH), 2·95 (OH),

6·13 and 9·3 μ (acetal), were identical with those of an authentic sample (m.p. 216–218°, $[\alpha]_D - 31°$) of the hemi-acetal (VII) prepared[12,19] from ajmaline (I) under identical conditions and identity was confirmed by comparison of the X-ray diffraction patterns.

Sodium borohydride reduction of ajmalidine (VIII) *to dihydrosandwicine* (VI).* Ajmalidine 10 mg[4] in 3 cm^3 of ethanol was treated with 30 mg of sodium borohydride at room temperature overnight. Addition of water and chloroform extraction gave after evaporation a crystalline residue which melted at 205–207° after two recrystallizations from methanol. The X-ray diffraction pattern and infrared absorption spectrum of this material were identical with those of dihydrosandwicine (VI).

Acknowledgement—The work at Wayne State University was supported by research grants from the American Heart Association and Eli Lilly & Co.

* This experiment was performed by Dr. S. C. Pakrashi at Wayne State University.

Tetrahedron, 1957, Vol. 1, pp. 338–342. Pergamon Press Ltd., London

NOTES

Chemistry of the sydnones—III*

FURTHER experimental observations on the decomposition of 3-phenylsydnone in alkaline solutions are described. When a reducing agent is also present, a highly coloured product, believed to result from isomerisation of glyoxylic acid phenylhydrazone, is formed.

A characteristic reaction of 3-phenylsydnone, not shared by most of the other sydnones, is its decomposition in boiling, weakly alkaline solutions.[1] The explanation of this reaction offered by Baker, Ollis and Poole[2] supposed the initial conversion of the sydnone into N-nitrosoanilinoacetic acid and subsequent decomposition of this, in accordance with the observation of Fischer,[3] into carbon dioxide and N-nitrosomethylaniline. In actual fact, the decomposition of N-nitrosoanilinoacetic acid is a more complex reaction. Carbon dioxide is evolved and a small proportion of volatile N-nitroso-compound can be isolated, but the principal product is a red tar which dissolves in concentrated sulphuric acid with a crimson colour. In contrast with this, 3-phenylsydnone decomposes under the weakly alkaline conditions specified to give carbon dioxide and a dark brown resin which dissolves in sulphuric acid with a greenish-brown colour, no volatile nitroso-compound being formed. Further, the addition of a little phenol to the solution entirely prevents the decomposition of the sydnone. This observation suggests that the reaction under discussion is essentially one of polymerisation. Other substances found similarly to inhibit the reaction were choral hydrate, *o*-phenylenediamine, resorcinol and anilinoacetic acid.

Treatment of 3-phenylsydnone with sodium hydroxide solution and zinc dust produces an intense crimson colour, which disappears on prolonging the reaction, together with small amounts of ammonia and aniline. Other reducing agents giving the same colour were ferrous hydroxide and sodium hydroxide, and hydrogen in the presence of finely divided nickel and sodium hydroxide.

The coloured substance is present in such small amounts that it could not be isolated, but it has the following definite properties:

(a) It is converted by further reduction to a colourless substance which is re-oxidised by air.

(b) It becomes yellow with acetic acid and strongly pink with mineral acids.

(c) It is adsorbed from alkaline solution by magnesium oxide, forming a brilliant, pink-violet lake.

The same colour appears, and apparently exclusively, in alkaline solutions in which phenyl hydrazine and sodium glyoxylate may be presumed to be present. For example, each of the following solutions warmed with a solution of phenylhydrazine hydrochloride rapidly becomes intensely crimson and the coloured substance present has the properties described above:

(a) Dichloroacetic acid boiled with excess of 2 N sodium hydroxide and cooled;

(b) An aqueous solution of oxalic acid, shaken with zinc dust, filtered and made alkaline;

(c) Glycollic acid heated with equal volumes of concentrated nitric acid and water and then made alkaline.

The crimson-coloured by-product obtained by Chattaway[4] during the oxidation of phenylhydrazine in alcoholic alkaline solutions probably results from the formation of a small amount of glyoxylate by oxidation of the alcohol.

Glyoxylic acid phenylhydrazone is easily prepared by boiling dichloroacetic acid and phenylhydrazine in alkaline solution and subsequently precipitating with hydrochloric acid. Recrystallisation from aqueous alcohol yields a product melting at 139°, identical with that prepared directly from glyoxylic acid. The crude product always gives crimson alkaline solutions, but purification is effected, without great loss, by boiling the alkaline solution with zinc dust or magnesium oxide. In the former

* Part II—*Rec. Trav. Chim.* **75**, 1080 (1956).

[1] R. A. Eade and J. C. Earl *J. Chem. Soc.*, 2307 (1948).

[2] W. Baker, W. D. Ollis and V. D. Poole *J. Chem. Soc.*, 307 (1949).

[3] O. Fischer *Ber. Dtsch. Chem. Ges.* **32**, 249 (1899).

[4] F. D. Chattaway *J. Chem. Soc.* **91**, 1323 (1907).

case the impurity is removed by reduction, in the latter by adsorption. The purified hydrazone does not give a crimson colour on dissolving in alkali, but the solutions become pink on standing or warming.

The general character of the coloured substance suggests that it is an azo compound with an acid, salt-forming group. Many such compounds among the azo-dyes, a simple example being phenylazophenol, dissolve in both strong acids and strong alkalis giving pronounced colours, whereas in weakly acid or alkaline solutions less intense colours are produced. The isomerisation, under some conditions, of glyoxylic acid phenylhydrazone to phenylazoacetic acid, $C_6H_5{\cdot}N{=}N{\cdot}CH_2{\cdot}COOH$, is quite probable and this substance would be expected to form highly coloured salts in both alkaline and strongly acid solutions.

Under alkaline conditions there is evidently a small amount of hydrolytic fission of 3-phenylsydnone at the 3:4 bond giving sodium glyoxylate as one product. When a reducing agent is present the other fragment from the fission is reduced to phenylhydrazine, which reacts with the sodium glyoxylate. Since 3-phenylsydnone is known to be reconverted in high yield into sodium N-nitrosoanilinoacetate by alkaline hydrolysis, the amount of fission at the 3:4 bond is undoubtedly small. The 4-halogenoderivatives, however, have been shown to undergo breakdown at the 3:4 link much more readily, although here the simultaneous production of aniline and sodium nitrite remains to be explained.[5]

The reactions of 3-phenylsydnone recorded above and in the earlier contributions of this series furnish examples of the fission of the sydnone ring, additional to those already well-known. It appears that acid hydrolysis, alkaline hydrolysis and reduction under a variety of experimental conditions are all effective in opening up the characteristic sydnone ring-structure. The different reagents attack different parts of the ring-system and some of the break-down reactions are almost quantitative. It can, therefore, be said that the sydnone ring is not a particularly stable structure, compared with the benzene or pyridine rings which are entirely unaffected by most hydrolytic reagents and do not readily undergo reductive fission. This being so, it is appropriate to comment on statements in the literature such as "... the sydnones are thus compounds exhibiting aromatic characteristics[2]". "The sydnones must be regarded as possessing a single hybrid structure of aromatic type[3]" and "... the known facts of sydnone chemistry indicate that the five-membered ring has aromatic properties and is planar; i.e. considerable delocalisation of the π electrons occurs[4]". It is clear that the authors of these statements do not regard "aromatic" as necessarily connoting a ring-structure stable against attack by chemical reagents.

EXPERIMENTAL

(a) *Resinification of 3-phenylsydnone by sodium acetate*

The sydnone (2 g) in water (150 ml) was boiled in a distilling flask while a 10 per cent solution of crystalline sodium acetate (10 ml) was added drop by drop during 15 min. The distillate contained a small amount of yellow oil which hardened on standing and did not give the Liebermann nitroso reaction. The principal product was a dark, non-volatile oil which solidified on cooling to a brittle resin soluble in concentrated sulphuric acid with a greenish-brown colour.

(b) *Resinification of 3-phenylsydnone with 0·1 N sodium borate*

The sydnone (0·186 g) was mixed with the sodium borate solution (25 ml) and heated to boiling. Rapid darkening and evolution of gas took place, with separation of a dark oil similar to that obtained with sodium acetate.

(c) *Effect of phenol on the resinification*

The sydnone (0·212 g), 0·1 N sodium borate (25 ml) and 1 per cent phenol solution (2 ml) were boiled under reflux for 30 min. The solution remained clear and pale yellow. On cooling and titrating with 0·1 N hydrochloric acid (methyl orange indicator), 24·95 ml were required, showing that no nitroso-acid had been formed. From the solution, on cooling, unchanged sydnone (0·11 g) crystallised out in almost white needles, m.p. 135°.

[5] W. Baker, W. D. Ollis and V. D. Poole *J. Chem. Soc.*, 1542 (1950).
[6] W. J. Orville Thomas *Chem. and Ind.*, 533 (1955).

(d) *Decomposition of* N-*nitrosoanilinoacetic acid in boiling aqueous solution*

Water (50 ml) and the acid (1·0 g) were boiled under reflux for 10 min. The steam-volatile product was distilled off and found to give the Liebermann nitroso reaction. The red, sticky tar remaining in the distilling flask did not give the Liebermann reaction, but dissolved in concentrated sulphuric acid with a crimson colour.

(e) *Alkaline reduction of 3-phenylsydnone*

The sydnone (0·162 g) was mixed with 0·5 N sodium hydroxide (100 ml) and zinc dust (0·2 g) and heated to boiling for 23 min, the volatile products being continuously collected in 1 per cent boric acid (25 ml). During the heating the solution acquired a crimson colour which subsequently disappeared. Titration of the boric acid with 0·1 N hydrochloric acid required 0·9 ml, corresponding to 9 per cent of the calculated possible yield of ammonia. The residual colourless solution was filtered from excess of zinc dust and exposed to air when it became strongly pink. Acidification with dilute acetic acid changed the colour to yellow, but on making alkaline again the pink colour was restored. Addition of hydrochloric or nitric acid gave a pink colour, irreversibly discharged on warming. Addition of magnesium sulphate to the alkaline solution gave an intensely coloured precipitate which was filtered off, yielding a colourless filtrate. In other larger experiments unsuccessful attempts were made to isolate the substance responsible for the pink colour. The highly coloured magnesium lake was gelatinous; after repeated washing and drying in air it gave a dull brownish-red mass, one sample of which was found to yield 53·7 per cent of magnesium oxide on ignition.

(f) *Preparation and purification of glyoxylic acid phenylhydrazone*

Dichloroacetic acid (2·88 g), phenylhydrazine hydrochloride (3·2 g) and sodium hydroxide (3·2 g) were dissolved in water (20 ml) and boiled under reflux for 1 hr. On cooling and acidifying with hydrochloric acid an oil was precipitated which soon solidified. Recrystallisation from aqueous alcohol gave 1·42 g of the phenylhydrazone melting at 135–139° which dissolved in alkali to an intensely crimson solution.

The crude product (1·0 g) was dissolved in 2 N sodium hydroxide (5 ml) and water (10 ml), zinc dust (1·0 g) being added. After boiling for 10 min the solution was cooled, filtered and acidified with hydrochloric acid. The precipitated phenylhydrazone after washing and drying (0·6 g) melted at 137° and dissolved in N sodium hydroxide without immediate pink colour.

Another sample of crude phenylhydrazone (0·5 g) was dissolved in 2 N sodium hydroxide (10 ml) and water (30 ml) and finely powdered, "light" magnesium oxide (1·5 g) added. After boiling for 30 min, the solution was filtered and the phenylhydrazone precipitated by acid. The product (0·35 g) melted at 141° and did not give an immediate pink colour when dissolved in alkali.

The assistance afforded to this work by a grant from Leverhulme Research Awards is gratefully acknowledged.

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Reduction of ketenes with lithium aluminium hydride—I. Diphenylketene

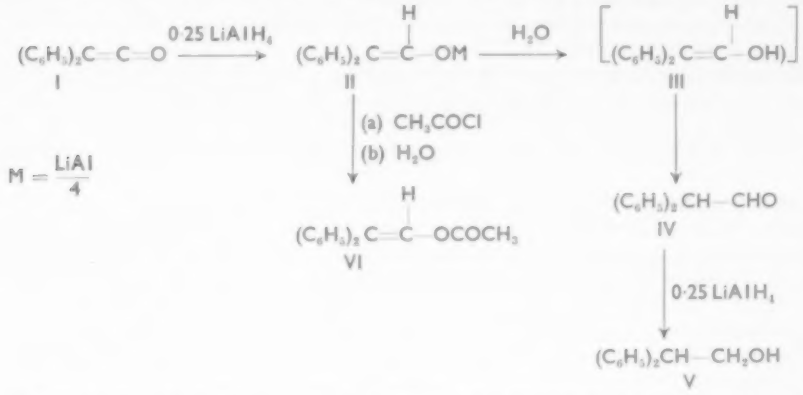
(*Received* 3 *June* 1957)

While alkyl ketene dimers have been reduced with lithium aluminium hydride to the corresponding β-ketocarbinols,[1,2] the reaction between free ketenes and the complex metal hydride, to our knowledge, has not hitherto been reported.

Lithium aluminium hydride attacks diphenylketene (I) by a 1:2-addition mechanism affording the complex II, which upon hydrolysis gives diphenylacetaldehyde (IV) in 93 per cent yield, probably via the intermediate enol III. Even in the presence of more than 0·25 mole of lithium aluminium hydride

per mole of ketene (e.g. with a 200 per cent excess), the reduction of I stops at the aldehyde (enol) stage, and no difference in yield was observed. However, the isolated diphenylacetaldehyde (IV) is readily further reduced with the same agent to the corresponding alcohol, diphenylethanol (V).

The existence of the complex II has been demonstrated by converting it, upon addition of acetyl chloride, to the enol acetate of diphenylacetaldehyde (VI), in 95 per cent yield.



The reduction of other ketenes with lithium aluminium hydride is now being investigated as well as the possibility of obtaining α-substituted aldehydes or vinyl compounds by reaction of intermediate complexes of type II with various agents, such as halogens, alkyl halides, alcohols.

EXPERIMENTAL*

Reagents. Diphenylketene (I) was prepared in 73 per cent yield from diphenylchloroacetyl chloride by means of zinc, according to the method of Staudinger.[3]† Stock solutions of lithium aluminium hydride in anhydrous diethyl ether were prepared[4] and the hydride content determined iodometrically.[5]

Reduction procedure. All reductions were carried out in the usual way, by adding dropwise a solution of the substance to be reduced in anhydrous diethyl ether to an ethereal solution of lithium aluminium hydride, at such a rate as to maintain gentle boiling of the solvent. After the addition had been completed, stirring was continued until the reaction mixture had cooled to room temperature. The reduction complexes were then carefully hydrolysed with water (ice cooling) and the inorganic precipitate dissolved in 10 per cent sulphuric acid. The reduction products were extracted with ether, the ethereal layer washed with 4 per cent aqueous sodium carbonate solution and with water, and the residue, after drying and evaporation of the solvent, was either distilled under reduced pressure or recrystallised.

Reduction of diphenylketene (I). Diphenylketene (11·2 g, 0·058 mole) in 50 cm³ of ether and 78 cm³ of lithium aluminium hydride solution (containing 0·0145 mole + 10 per cent excess of hydride) gave 10·6 g (93·1 per cent) of *diphenylacetaldehyde* (IV), b.p. 178–180°/12·5 mm.[6] Semicarbazone, m.p. 158–160°;[7] oxime, m.p. 111°;[8] 2:4-dinitrophenylhydrazone, m.p. 144–145°.[9]

The same reduction with a 200 per cent excess of hydride afforded diphenylacetaldehyde in 92·5 per cent yield.

* All melting points are uncorrected.

† This procedure, in our hands, appeared to be superior to the one described in *Org. Syntheses* Coll. Vol. 3, p. 356 (1955).

[1] R. L. Wear *J. Amer. Chem. Soc.* **73,** 2390 (1951).
[2] A. S. Spriggs, C. M. Hill and G. W. Senter *J. Amer. Chem. Soc.* **74,** 1555 (1952).
[3] H. Staudinger *Ber. Dtsch. Chem. Ges.* **38,** 1735 (1905).
[4] W. G. Brown *Org. React.* **6,** 470 (1951).
[5] H. Felkin *Bull. Soc. Chim. France* 347 (1951).
[6] A. Béhal and M. Sommelet *C. R. Acad. Sci., Paris* **138,** 91 (1904).
[7] E. P. Kohler and N. L. Drake *J. Amer. Chem. Soc.* **45,** 1281 (1923).
[8] P. Lipp *Liebigs Ann.* **449,** 26 (1926).
[9] T. A. Favorskaya and L. A. Remizova *J. Gen. Chem.* (*U.S.S.R.*) **23,** 817 (1953).

Reduction of diphenylketene (I) *with addition of acetyl chloride*. Diphenylketene (8·0 g, 0·041 mole) in 50 cm³ of ether was added to 54 cm³ of an ethereal solution of lithium aluminium hydride (containing 0·01 mole + 10 per cent excess of hydride), and the resulting complex was treated dropwise with 3·6 g (0·041 mole + 10 per cent excess) of acetyl chloride in 10 cm³ of anhydrous ether. The reaction mixture turned yellow and a granular precipitate separated. After heating 30 min to boiling, the reaction product was hydrolysed and worked up as described above to yield 9·25 g (94·7 per cent) of the *enol acetate of diphenylacetaldehyde* (VI), m.p. 58° [10*] (from dilute ethanol) (Found : C, 80·60; H, 5·98. $C_{16}H_{14}O_2$ requires C, 80·65; H, 5·92 per cent).

The same enol acetate (m.p. 58°) was obtained in 78·2 per cent yield (9·5 g) by heating 11·8 g (0·051 mole) of diphenylacetaldehyde with 8 cm³ (0·081 mole) of acetic anhydride and 1·4 g (0·017 mole) of anhydrous sodium acetate for 1 hr at 160–165°, pouring the cooled mixture into water and extracting the oily layer with ether.[10*] A mixture of both enol acetates gave no depression in melting point.

Reduction of diphenylacetaldehyde (IV). Diphenylacetaldehyde (6·0 g, 0·031 mole) in 50 cm³ of ether was reduced with 45 cm³ of lithium aluminium hydride solution (containing 0·008 mole + 10 per cent excess of hydride) to produce 5·95 g (97·5 per cent) of *diphenylethanol* (V), b.p. 178–180°/13 mm, m.p. 59–61°[11,12] (from petroleum ether). Benzoate, m.p. 90°[11].

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* This author gives a m.p. of 59° for the enol acetate. However, the experimental procedure for its preparation and analysis are not reported.

[10] M. Tiffeneau *C. R. Acad. Sci., Paris* **150**, 1181 (1910).
[11] P. Ramart and P. Amagat *Ann. Chim.* [10] **8**, 263 (1927).
[12] E. Bergmann *J. Chem. Soc.* 412 (1936).

Tetrahedron, 1957, Vol. 1, pp. 343–344. Pergamon Press Ltd., London

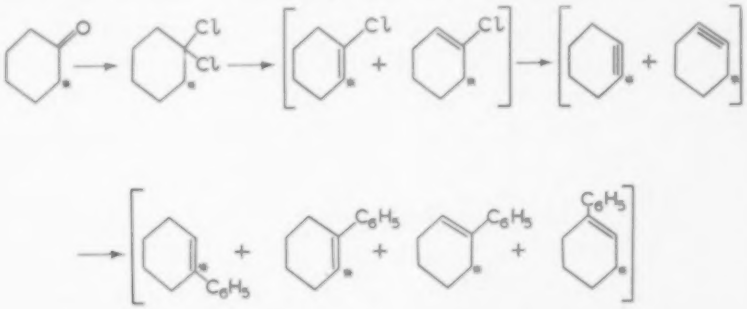
PRELIMINARY COMMUNICATION

Evidence for *cyclo*hexyne as an intermediate in the coupling of phenyllithium with 1-chloro*cyclo*hexene*

(*Received* 23 *July* 1957)

ELIMINATION-ADDITION mechanisms involving "benzyne"-type (C_6H_4) intermediates have been established for the rearrangements which occur in the amination of non-activated aryl halides,[1] high temperature alkaline hydrolysis of aryl halides[2] and the coupling of phenyllithium with aryl halides.[3] Wittig and Harboth[4] have reported small yields of 1-phenyl*cyclo*hexene from the coupling of phenyllithium with 1-chloro*cyclo*hexene and it appeared possible that this reaction might well proceed by way of *cyclo*hexyne as an intermediate. Of interest in this connection is the report by Favorsky and Boshowsky[5] that a *cyclo*hyexne trimer (dodecahydrotriphenylene) is formed in the reaction of 1,2-dibromo*cyclo*hexene with sodium.

We have studied the conversion of *cyclo*hexanone-2-^{14}C† to 1-phenyl*cyclo*hexene by way of 1,1-dichloro*cyclo*hexane and 1-chloro*cyclo*hexene. If all of the reaction were to proceed by intermediary formation of *cyclo*hexyne (and kinetic isotope effects were absent) then 25 per cent of the resulting 1-phenyl*cyclo*hexene would be expected to have the ^{14}C-label at the 1-position. This prediction is based on the following considerations. *cyclo*Hexanone-2-^{14}C with phosphorus pentachloride should yield 1,1-dichloro*cyclo*hexane-2-^{14}C without rearrangement. Dehydrohalogenation would then yield a 1 : 1 mixture of 1-chloro*cyclo*hexene labeled at the 2- and 6-positions. Coupling of this mixture with phenyllithium by any non-rearranging reaction such as formulated earlier[4] would lead to 1-phenyl*cyclo*hexene labeled at the 2- and 6-positions without formation of 1-phenyl*cyclo*hexene-1-^{14}C. On the other hand, if the phenyllithium were to effect an elimination of hydrogen



* Supported in part by the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgement is hereby made to the Donors of the Fund.

† Obtained from the Radiation Laboratory of the University of California on allocation by the U.S. Atomic Energy Commission.

[1] J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith and C. W. Vaughan *J. Amer. Chem. Soc.* **75,** 3290 (1953); J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr. and L. A. Carlsmith *Ibid.* **78,** 601 (1956).

[2] J. D. Roberts, A. T. Bottini, and D. A. Semenow *Science* **122,** 881 (1955); A. T. Bottini and J. D. Roberts *J. Amer. Chem. Soc.* **79,** 1458 (1957); A. Lüttringhaus and D. Ambros *Ber. Dtsch. Chem. Ges.* **89,** 463 (1956).

[3] G. Wittig, G. Pieper and G. Fuhrmann *Ber. Dtsch. Chem. Ges.* **73,** 1193 (1940); G. Wittig *Z. Angew. Chem.* **69,** 245 (1957); R. Huisgen and H. Rist *Naturwissenschaften* **41,** 358 (1954); *Liebigs Ann.* **594,** 137 (1955); E. Jenny and J. D. Roberts *Helv. Chim. Acta* **38,** 1248 (1955).

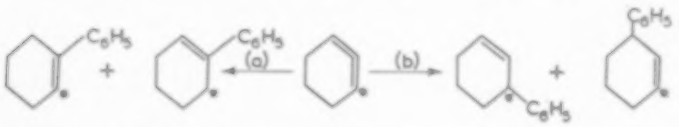
[4] G. Wittig and G. Harboth *Ber. Dtsch. Chem. Ges.* **77,** 306 (1944).

[5] A. E. Favorsky and W. Boshowsky *Ann. Dtsch. Chem. Ges.* **390,** 122 (1912).

chloride from the labeled 1-chloro*cyclo*hexene, a 1 : 1 mixture of *cyclo*hexyne-1-^{14}C and *cyclo*hexyne-3-^{14}C would be formed. Since each differently labeled *cyclo*hexyne can add phenyllithium in two equally probable ways, one predicts formation of 25 per cent each of the labeled 1-phenyl-*cyclo*hexenes with ^{14}C at the 1-, 2-, 3-, and 6-positions.

*cyclo*Hexanone-2-^{14}C with phosphorus pentachloride followed by elimination of hydrogen chloride[6] afforded 40 per cent of 1-chloro*cyclo*hexene-2-and-6-^{14}C. The reaction of the labeled 1-chloro*cyclo*hexenes with 2·5 moles of phenyllithium in ether in a steel bomb at 150° gave 28 per cent of 1-phenyl*cyclo*hexene-*x*-^{14}C. The product was characterized as 1-phenyl-2-(2,4-dinitrophenylmercapto)-*cyclo*hexene-*x*-^{14}C, m.p. 139·5-140·5°. Oxidation of the latter substance with sodium permanganate gave the 1-carbon and phenyl group as benzoic acid. This benzoic acid had a ^{14}C assay of 0·0280 ± 0·0005 μc per mole which was 23 ± 0·7 per cent of the activity (0·1217 ± 0·0015 μc per mole) of the dinitrophenylmercapto derivative. Thus 23 per cent of 1-phenyl*cyclo*hexene labeled at the 1-position was formed in the reaction as compared to 25 per cent predicted for the elimination-addition mechanism involving *cyclo*hexyne as an intermediate. The small difference between the experimental and theoretical results may be due to the incursion of some non-rearranging reactions or very reasonable inter- and intra-molecular ^{14}C-isotope effects[7] in the preparative or degradative sequences. The validity of the degradative scheme was checked by adding phenyllithium to *cyclo*hexanone-2-^{14}C and dehydrating the carbinol with sulfuric acid. The dinitrophenylmercapto derivative of the resulting 1-phenyl*cyclo*hexene-2-^{14}C gave benzoic acid with about 0·1 per cent of the total activity.

1,2-*cyclo*Hexadiene-1-^{14}C might result from elimination of hydrogen chloride from the labeled 1-chloro*cyclo*hexene with phenyllithium. Such an allenic intermediate is unlikely to be important since, if it were to add phenyllithium so that the phenyl combined with the 2-carbon, equation (a),



no 1-phenyl*cyclo*hexene-1-^{14}C would be formed. If the phenyl were to add to the 1- or 3-carbons, equation (b), then the final product would be 3-phenyl*cyclo*hexene instead of the isolated 1-phenyl-*cyclo*hexene.

Contribution No. 2230 from the
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[6] M. Mousseron and R. Jacquier *Bull. Soc. Chim. Fr.* 648 1950.
[7] G. A. Ropp *Nucleonics* **10**, (10), 22 (1952).

BOOK REVIEWS

The Encyclopedia of Chemistry. Edited by GEORGE L. CLARK, GESSNER G. HAWLEY, and WILLIAM A. HAMOR, Reinhold Publishing Corporation New York 1957. xvi + 1037 pp., $19.50, £7. 16s.

THIS large volume contains somewhat over eight hundred short articles contributed by more than five hundred chemists and allied scientists. Some of these men are particularly distinguished in the fields about which they write: for example E. W. R. Steacie on Free Radicals, C. P. Smyth on Dipole Moments, H. Eyring on Reaction Rates, J. E. Hildebrand on Solubility, and G. T. Seaborg on Transuranium Elements to mention just a few at random. The articles vary from a short paragraph to three or four two-columned pages; they all have cross-references but unfortunately no bibliography. Although some of the articles are of the very highest quality the standard is very uneven and there are some quite extraordinary overlaps and omissions. Alkaloids are dismissed in a page and a half of muddled writing containing some factual errors, while glycols are spread over two and a half pages. Over a page is devoted to quinoline, while iso-quinoline is not mentioned and pyridine receives a few lines in the article on Heterocyclic Compounds the total length of which is three-quarters of a page. A curious overlap occurs in the articles on Hydrolysis and Saponification. The different contributors have chosen the same reaction (the hydrolysis of tri-stearin) as their example yet, in spite of copious cross-references, neither article refers to the other. On the whole Organic Chemistry is particularly unevenly treated, although there are some bad articles and odd omissions in other fields. The essay on Acids, apart from being most inexact, fails to mention Brönsted, Lowry, or Lewis, or the concepts connected with their names. Only some of the elements are listed (surely it would be better to include them all, even if many could be discussed in two lines?), and the selection is strange, for example Francium is included while Argon is not. A desirable feature is the inclusion of brief biographies of famous chemists such as Dalton, Berzelius, and Willstätter, also included are E. G. Acheson, H. H. Dow, and E. W. Hilgard, while J. L. Gay-Lussac, Emil Fisher, and G. N. Lewis are not! It would be possible to enumerate many more minor errors and strange omissions but sufficient has been said to indicate the main weaknesses of the book. A larger editorial board including chemists from all the major branches of chemistry would seem essential to obtain anything like an even coverage of the vast field attempted. Although as a complete unit the book must be regarded as a failure, it does contain some excellent essays, (e.g. Chemical Literature by E. J. Crane) and some masterly condensations of complex subjects (e.g. Carbohydrates by Whistler and Corbett). The printing is excellent, there are very few typographical errors, and the paper and binding are good.

J. M. TEDDER

E. CARTMELL and G. W. A. FOWLES: **Valency and Molecular Structure**. Butterworths Scientific Publications, London, 1956. 256 pp., 32s. 6d.

As the authors state in their preface "This book is written by chemists for chemists," and a study of the book leaves no doubt that the authors have produced a most useful text. The subject matter is divided into three parts. Part I on Quantum Theory and Atomic Structure discusses the experimental foundations of the Quantum Theory and its application to isolated atoms. The application of the theory to atoms in combination is described in Part II on the Quantum Theory of Valency; the approximation methods of valency bond and molecular orbital methods are discussed, and both are used in the discussion on directed valency. Part III describing the Application of the Principles of Chemical Bonding constitutes almost half the text, and contains Chapters on recent work concerning bonding in the solid state, the structures of some simple inorganic compounds, complex compounds, and electron-deficient molecules.

The authors have certainly justified their prefatory remark—the honours student in chemistry will find the text of considerable assistance and the postgraduate will find the discussions of recent work in Part III stimulating.

The Authors and Publishers are to be congratulated on the production of a most interesting text which should appeal to a wide circle of chemists. The subject matter is well illustrated with tables and diagrams.

H. STEPHEN

LOUISE KELLEY: **Organic Chemistry** (2nd Ed.). McGraw-Hill, New York, London, 1957. viii + 757 pp., 56s. 6d.

THIS volume by Louise Kelley is a revision of *Organic Chemistry* published by this author in collaboration with Albert Hill in 1943. The aim of the author, stated in the preface, is to present a textbook suitable for a first year course and comprehensive enough to serve later as a reference book for the student. This aim has been achieved in that the first year course is more than adequately covered and the inclusion of chapters on Polynuclear hydrocarbons, Dyes, Terpenes, Heterocyclic compounds; Alkaloids; Steroids, Plant pigments, and Vitamins should prove useful to the better student.

The Introduction is followed by a chapter on bond structure which as well as dealing with electronic structure, types of bonds, bond angles, and electronic displacement, has some excellent explanatory tables from the works of Ingold, Pauling and Ferguson. Reaction mechanisms are not introduced until Chapter 12 by which time the student has become familiar with organic chemistry, having studied aliphatic hydrocarbons (including rubber) alcohols, ethers, acids, and esters. Chapter 13 deals with Molecular Orbital Theory, again a good stage at which to introduce these ideas to the new student.

The section on Stereochemistry is weak. Absolute configuration is not mentioned and we are told that "there is no way of determining the spatial configuration which is responsible for a dextrorotatory or levorotatory effect". One feels that even in textbooks for first year students it should be clear that, as shown by Bijvoet and his co-workers, the arbitrary configuration assigned to D(+)-glyceraldehyde represents the absolute configuration of the molecule. Again diagrams in this chapter are not good, which is surprising as those in the rest of the book are excellent.

The aromatic portion of the text is, as is usual, introduced by a chapter on Benzene and its Homologs and here, as on the aliphatic side, there is a modern approach. The following section headings may best illustrate the manner in which the electronic effects are discussed—orientation and activation in the benzene ring; explanation of orienting and activating effects in aromatic substitution; effects of *ortho*- and *para*-directing groups.

About 80 pages have been allocated to more advanced topics. Under Dyes are discussed the modern theory of colour and the dyeing of such fibres as cellulose acetate, nylon, Orlon, and Dacron. Under Heterocyclic Compounds are descriptions of sulpha drugs, a note on penicillin, and the formulae for aureomycin and terramycin.

To be commended is the attention to detail in the following—the numbering of sections in each chapter, making for easy cross-reference; the short biographical notes throughout the text; a good variety of problems, suggested reading, and references to recent literature at the end of the various chapters.

On the whole, in the opinion of the reviewer, a competent work in which the author has achieved her aims.

EVA M. PHILBIN

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OBITUARY NOTICE

The Editors and Publishers have learned with very great regret of the untimely death of Professor M. S. Kharasch in Copenhagen on 10 October. Pending the appointment of a new Executive Editor for the United States, American contributors are asked to direct manuscripts to the Joint Chairman of the Honorary Editorial Advisory Board, Professor R. B. Woodward, Department of Chemistry, Harvard University, Cambridge, Massachusetts.

Papers to appear in forthcoming issues

R. B. WOODWARD, F. E. BADER, H. BICKEL, A. J. FREY and R. W. KIERSTEAD: The total synthesis of reserpine

A. BURAWOY: Theory of electronic spectra of organic molecules

S. SWAMINATHAN, ROBERT S. STOBAUGH and MELVIN S. NEWMAN: Intermediates for steroid synthesis

F. WINTERNITZ and C. BALMOSSIÈRE: Synthèses de substances polycyclignes (IXème mémoire) Obtention d'α-decalones substituées par condensation dienique

JANET ALLINGER and NORMAN L. ALLINGER: The conformers of 2-bromo*cyclo*hexanone

BARNEY J. MAGERLEIN and JOHN A. HOGG: The synthesis of a ring 9//10-secosteroids from unsaturated 3,11-diketo steroids

T. S. WHEELER, J. E. GOWAN, G. J. MACMAHON, S. O'CLEIRIGH, S. P. MACGIOLLA RIOGH, and E. M. PHILBIN: A synthesis of 6:8-dihydroxyflavone

L. VAGHA and G. OCSKAY: Untersuchungen über Furan-Verbindungen—V. Über dei Herstellung und Konfiguration von einigen Furyl-keloximen

L. VARGHA and G. OCSKAY: Untersuchungen über Furan-Verbindugen—VI. Stereospezifische Ringöffnungsreaktionen in der Furan-Reihe

L. VARGHA and G. OCSKAY: Untersuchungen über Furan-Verbindungen—VII. Umwandlung von 2-acyl-benzofuran-Derivaten in Chromanol-Derivate

S. WINSTEIN and J. TAKAHASHI: Neighboring hydrogen, isotope effect and conformation in solvolysis of 3-methyl-2-butyl *p*-toluenesulfonate

R. H. JAEGER: Analogues of male sex hormones

CARL DJERASSI, R. NAKANO and J. M. BOBBITT: Alkaloid studies—XX. Isolation and structure of two new cactus alkaloids, piloceredine and lophocerine

T. URBANSKI and J. HACKEL: Some remarks on the theory of nitration

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Figure 2 on p. 220 has been transposed with Fig. 3 on p. 216.

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